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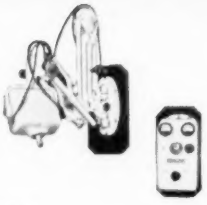

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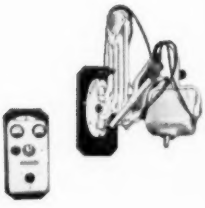

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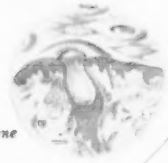

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1. Bednar, G. A.: South. M. J. 46:298 (March) 1953.
2. Wright, C. S., et al.: A. M. A. Arch. Dermat. & Syph. 67:125 (Feb.) 1953.
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4. Andrews, G. C., et al.: J. A. M. A. 146:1107 (July 21) 1951.

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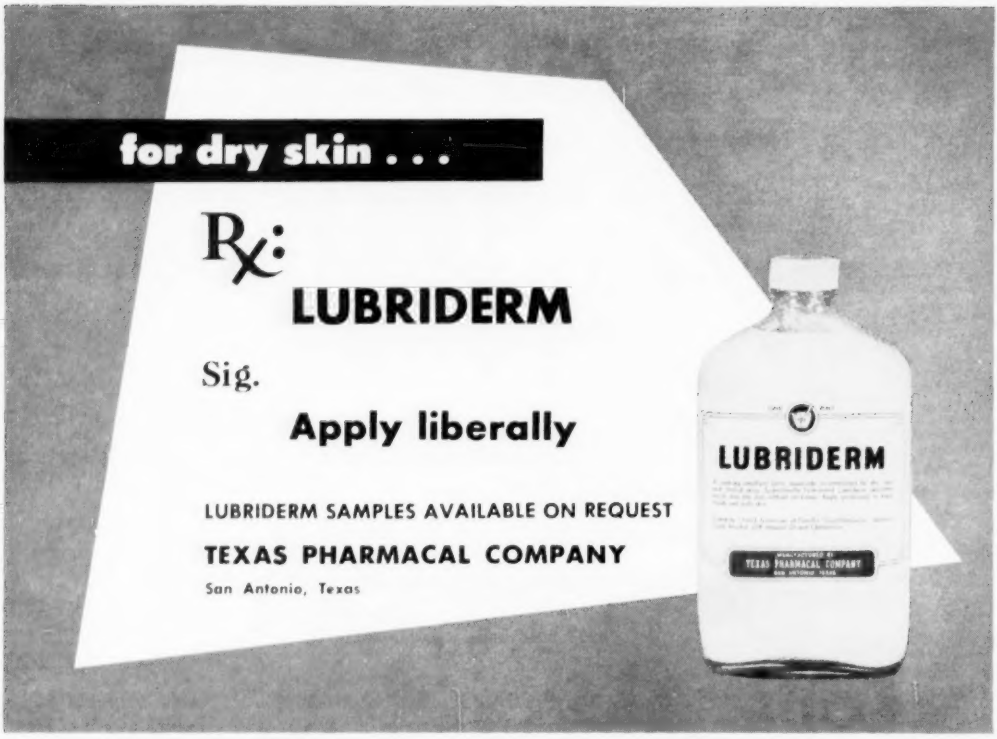

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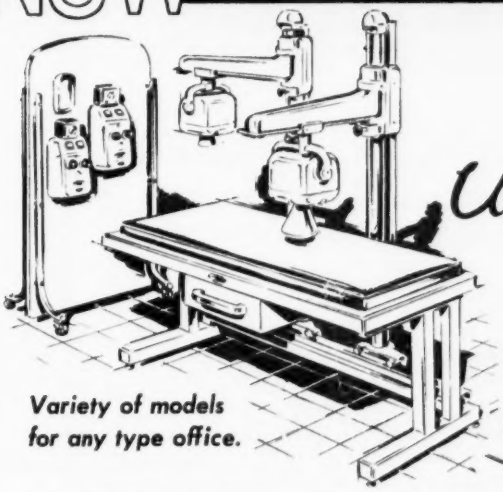

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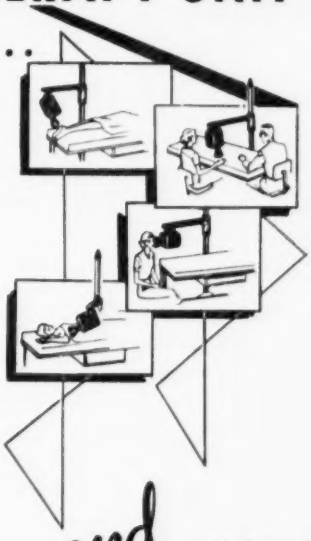

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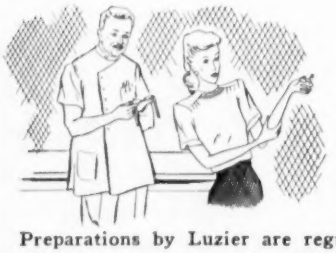

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UNDERGRADUATE INSTRUCTION IN DERMATOLOGY

A Critique

HERBERT S. ALDEN, M.D.
JACK W. JONES, M.D.
AND
PHILIP H. NIPPERT, M.D.
ATLANTA

TO THOSE of us living in that uneasy middle generation, forbidden to be modern and reluctant to be mellow, there is a growing feeling of guilt that we are in part responsible for what appears to be the inadequate training of the undergraduate student in the specialties of medicine.

There is then, understandably, a great desire among us to reevaluate our concepts and our goals in the light of that some have been pleased to call "the changing order." Nowhere among the medical specialties is this desire greater than among the dermatologists, as witnessed by the discussions of Wile,[1] Cole,[2] Stokes,[3] Lane,[4] Cipollaro,[5] and those engaged in the organization and operation of the American Board of Dermatology and Syphilology. Within the many papers on medical education there is abundant evidence of a growing dissatisfaction with existing methods of instruction.* On the other hand, there has been for many years a perennial criticism of the patent inadequacies of the medical college curriculum; until now there is general agreement on one point only: that it is impossible to expect a student at graduation to be an adequate practitioner of medicine. Of course, there have been many changes, brought about much by the phenomenal growth in the natural sciences, but our present massive medical curriculum has grown more by accretion than by design.

In 1870, Jacob Bigelow told his graduates of Harvard Medical School to have no fear of their adequacy in their profession, since in two years they had learned all there was to know of medicine and surgery. Soon the orthodox course in medicine had evolved from two to three years and then to four, and in the 1920 to 1930 period the fifth year, of internship, was a matter of expectancy, until now the years of training extend much further. Obviously, knowledge in medicine has extended far beyond the scope of one person. And yet the curricula course of study remains at four years' duration. It is therefore quite apparent that we are now obliged to impart less and less of a more expanding medical knowledge within the same space and time. Is it any wonder that we have a feeling of frustration?

From the Department of Dermatology, Emory University School of Medicine.

Read at the Seventy-Third Annual Meeting of the American Dermatological Association, Inc., Lake Placid, N. Y., June 11, 1953.

* References 6 to 11.

The past 25 years have seen many attempts to bring a measure of competence in teaching at least some of this expanding scientific knowledge to the undergraduate student by widely dividing the medical curriculum among the various specialties. Instruction has been compartmentalized to such a degree that the student finally often confronts an ill patient as he would a cold fish, to be sliced into component parts and served upon the altar of science without either salt or savor. Some of the specialties, such as dermatology, seem to have suffered the yoke of neglect in this scientific scheme and have in some instances been wholly obliterated as teaching units.

Stung by this high professorial and curricular snubbing, the dermatologist sometimes asks for a greater measure of the dwindling teaching time and something more of the thinning budget of his medical school. He marshals strong statistics to show that the general practitioner is poorly trained in the fundamentals of diagnosis and care of diseases of the skin—that various simple dermatoses took up an exasperatingly large portion of the disabilities of our armed forces in World War II—that the general public now demands much more from its physicians than a confession of ignorance of skin disease, more especially when 10% of its troubles involve its hide. Therefore, he asks that he have more of the teaching time in the undergraduate years of medical college.†

But these discomforts and lamentations of the teachers of dermatology are not new. Exactly 26 years ago a magnificent discussion of medical education in dermatology was presented to this association ‡ by a triad of great teachers, who are now among the "Elder Statesmen" of the American Dermatological Association, in which one can clearly ascertain the beginnings of the American Board of Dermatology and Syphilology. Some of the thoughts and statements of Dr. Udo Wile,[1] Dr. Howard Cole,[2] and Dr. John Stokes [3] sound strangely familiar to us today and are echoed in much of the very recent literature pertaining to medical education.

Perhaps it is well to reflect on some parts of the questions asked by Stokes,[3] and above all to ask ourselves, Just what are the essential functions of a medical school within our changing order? To what extent is dermatology to be taught as such to medical students? Which method of undergraduate teaching serves the interest of the patient better: that which makes the practitioner so much a pseudodermatologist that he thinks he needs a specialist only to carry out some manipulative procedure, or that method which, while it leaves him handicapped in diagnosis, gives him general knowledge of the field in the obvious situations and allows him some competence in the care of simple skin eruptions?

What are the essential functions of the medical school in our changing order? Since there is by now general agreement that in our times it is not possible to expect a student at graduation to be an adequate practitioner of medicine, we cannot answer this question simply and easily by saying its primary function is to teach a student to "recognize and treat simple conditions that occur in everyday practice."[5] Such an answer is simplification of a tremendous order, since "such conditions" make up the bulk of mankind's discomforts and leave no room in the school for the study of the wisdom of the human body and comprehension of its effects on the body politic.

† References 4 and 5.

‡ References 1 to 3 (The Teaching of Dermatosyphilology).

Obviously, our medical schools exist to teach students so that they may obtain there an M.D. degree, which is required of all physicians and which is not offered except in an approved school of medicine. But this is not all—they must teach "great medicine" [16] also. It carries a greater responsibility in teaching comprehensive medicine which will provide for the medical student better opportunities to learn how to serve the patient more effectively. After all, servitude to the welfare of the patient is the final goal. But in our changing order the medical school has a still further responsibility beyond its primary obligation to the undergraduate in that it must participate in all levels of medical education and patient care, including a part in discovery and application of new knowledge. Further, it must train and educate other health and medical personnel. In all this the dermatologist should play a part.

While it is not possible completely to disassociate these functions of a medical school, we do in this discussion wish to limit ourselves to undergraduate instruction in dermatology, and, as near as possible, limit our field of inquiry to our own geographic area. With this limitation in mind we ask ourselves: To what extent is dermatology as such to be taught to the medical student in this changing order? And within these limitations, by what method?

Sir Francis Bacon, many years ago, observed, "The contemplation of things as they are—without substitution or imposture—without error or confusion—is in itself a nobler thing than a whole harvest of inventions." We believe that this viewpoint is even more important in our time of jumpy conclusions. We appear to be past the point where we need discussion of what we hope to do or what we might do. We need more discussion of what we are doing. In this light the teaching staff of Emory University School of Medicine have sought an answer to these questions.

It has been said that the ideal university is made up of Dr. Mark Hopkins astraddle one end of a log and the student on the other end. As satisfactory as this might be for the student, such a preceptorship in medical college is no longer possible. Add to one end of this log some 60 not-so-avid students and the physician on the other end will have a difficult time, even if he is helped and supported by a half dozen assistants. Now replace this log with a modern medical school "curriculum" (which literally means "a running" or "a race course") and one can visualize a new significance in the present plight of the student. Now make the teacher a part-time voluntary instructor, whose main interest lies in other fields, and you have the general picture of instruction in dermatology in our medical school.

Emory University is not an old university and is, enrollment-wise, a small university. Its stated objective is to continue to be a small university, its main purpose being to grow stronger rather than bigger.§ In its medical school the teaching of cutaneous medicine really began in the 1920's to a third-year class, averaging 50 students, with a series of textbook lectures as tiresome and uninspiring to the lecturer as they were to the student. In addition, he received in his fourth year a more or less elective participation in the outpatient skin clinic. The teaching staff was voluntary and irregular in attendance, but much practical instruction was given. Since the dermatologist was accepted because he was

§ Office of the President of Emory University: Some Basic Principles and Their Implication, Bulletin to the Faculty, February 13, 1953.

needed, not because he was wanted, he received little help in teaching from the faculty. He recognized the obvious inadequacies and hoped for better in the future. During the ensuing years, when the local population grew rapidly and the outpatient population increased, the volume of teaching in all medical fields grew by accretion, but the physical facilities remained approximately the same. The teaching of great medicine was becoming bafflingly compartmentalized, and the curriculum was really a "race course" for the student and for the voluntary teaching staff, who must needs treat and keep records on the clinic patient.

Since our part-time voluntary teacher in dermatology must divide his allegiance among his office patients, from whom he derives his income, the treatment of the indigent in the clinic, and the medical students, the student in many ways has to get what he can while the patient is cared for in haste.

This is not to say by any means that there has been no progress in medical education at Emory University in these past 30 years. On the contrary, it has been vast in all phases of medical education, both in extent and in depth. The budget has increased from $80,000 to over $1,000,000, which covers and includes laboratories, research, hospital teaching facilities, and an increase in the paid clinical faculty from none to 34. But the physical facilities at our city teaching hospital have not kept pace either with the population increase or the medical school improvements.

Now, in the 1950's, we are teaching 73 students in each of the third and fourth years, with 34 full-time paid faculty members in these years. None of these full-time men are on the dermatology staff, and the dermatology clinic space and time has not changed. We now have seven practicing dermatologists on the staff, who each give two hours a week to clinical instruction in the outpatient departments, but, while there is semiprofessorial rank, dermatology remains under the department of medicine.[12] We manage creditably to take care of over 8,000 patients a year and instruct each third-year student in basic clinical dermatology, in addition to giving 10 hours of lectures on basic principles, and give the fourth-year student 48 hours of clinical dermatology.

During our entire teaching careers at Emory University School of Medicine the method of teaching the individual student has changed but little. We have never been able to discover the time or space in the curriculum for broadening the teaching, and without the physical space and finances for postgraduate instruction, we have had a sneaking suspicion that it was neither useful nor desirable. Realizing these limitations, we have made no real attempts to teach any of the more complicated dermatologic procedures or the finer points of dermatology. The student has been instructed to observe and examine the patient from an objective standpoint, such as type of skin lesion, location, and arrangement, with its egression and regression of inflammation and growth. The resounding and sonorous terminology of the Viennese school, so dear to our hearts, has been studiously shunned in favor of the study of the elementary and evolutionary changes by having the student see them in the flesh. We have never felt it necessary or desirable to include instruction in microscopic changes in the skin in the work of the undergraduate. Discussions of treatment are just as simple, stressing the use of soothing local medicaments, not relating the intricacies of such manipulative procedures as x-irradiation or electrocauterization. Through-

out these years we have always strived for greater depth and repetition in the demonstration of a few common skin diseases, rather than broadening our field into the rare and controversial skin eruptions.

Now, as to the lectures in dermatology during this period, we quote from a personal communication from a general practitioner whose opinion was asked. He makes some pertinent remarks about lectures in general, as follows:

> These [lectures] are for the most part a vast waste of time. The courses are completely without attempted correlation. Many of those entrusted with the task of lecturing are entirely incompetent, partly because they are not able to lecture adequately, but largely because they are not sufficiently trained in the methods of teaching. . . . The result is a large amount of useless repetition, contradiction, inconsistencies, and omissions, which is very boring to the student.

Some of you may say, with good reason, that this is not a creditable record for a department of dermatology within these 25 years of scientific developments. Certainly it does no more than approach the four fundamental requirements for real success in a teaching program recently promulgated by Wile.[13] In fact, our minimum teaching program smacks of heresy in that (1) we do not have a director of full professorial rank; (2) we do not have an associate professor on a part- or a full-time basis, or interns, or assistant residents, or technical assistants, or research laboratories; (3) we do not have a budget at all; (4) we do have qualified incumbents on the teaching staff, with a background in internal medicine and some convincing and imaginative teachers.

Heretical as it may seem, we cannot in our circumstances contemplate this ideal in the near future, nor do we believe it is necessary or useful in a medical school which is engaged solely in undergraduate instruction.

But, after all, no self-criticism of teaching should be complete without the viewpoint of those who had been taught. We have said that it is not the purpose of the inquiry to judge the student but that we must accept him as he is and not as we might wish him to be. But since our educational system of forced feeding has already been judged as inept and the American student has more than once been indicted for his immaturity, we must keep this in mind in evaluating his answers to questions of medical education.‖ After graduation in medicine, does he believe that his instruction in dermatology was adequate to his needs? What instruction did he miss or lack, and what changes in instruction would he favor? As a practitioner of medicine, does he wish further instruction in dermatology?

To get some of these answers a questionnaire was sent to three groups of doctors, all of whom had passed beyond the responsibilities of their medical schools: (1) recent graduates—interns and residents in local hospitals; (2) graduates of Emory University School of Medicine of the past four years, and (3) physicians in general practice of 5 to 10 years' duration. A total of 139 physicians answered this questionnaire.

Answers to the questions were as follows:

1. Do you think you had adequate medical teaching in dermatology? No, 75%
2. Would you favor a change in the curriculum relating to dermatology? Yes, 80%
3. What type of change would you favor?
   (*a*) More hours of lecture. Yes, 17.5%
   (*b*) More hours of group outpatient teaching. Yes, 51%

‖ References 14 and 15.

(*c*) More detailed instruction on small groups of patients. Yes, 51%

(*d*) More time for personal-patient responsibility and care. Yes, 44%

(*e*) More outpatient experience. 54% answered Yes.

(*f*) More visual aids. Yes, 40%

4. What instruction did you lack or miss?

(*a*) Opportunity to examine patients closely. Yes, 37%

(*b*) Opportunity to treat patients individually. Yes, 51%

(*c*) Opportunity to have problems discussed or explained by instructor. Yes, 44%

5. In the light of your experience in the practice of medicine would you have liked more instruction in dermatology? Yes, 60%

6. Would you have sacrificed in other specialties to have obtained this? Yes, 53%

7. Would you be interested in a postgraduate course in dermatology? Yes, 67%

The chief general criticism volunteered by many physicians who answered our questionnaire dealt with the large quantity of duplicating laboratory work, history taking, and part-time intern duties which in recent years has been expected of the student. As a fourth-year student, he may, in fact, do much substitution work for the hospital which is understaffed with interns and residents.

We can take heart from, but not pride in, the fact that while 79% of Emory University graduates thought their undergraduate teaching in dermatology was inadequate, 70% of the graduates of other schools thought likewise. It appears that regardless of the medical school three-fourths of the students considered their instruction in dermatology lacking, and all of these favored a change in the curriculum in which personal contact with the patient in examination and in treatment seemed most important. Over half of those who now realize they would have liked more instruction in dermatology would have sacrificed some other specialty to obtain it. And, lastly, 67% now desire postgraduate instruction in dermatology.

We have for some time felt that the instruction in dermatology was neither adequate nor sufficient in itself to produce in all students a sense of comfort and confidence when confronting a patient with an unknown skin disease. Within our limited means of time, space, and help we have attempted changes in our curricular approach to obtain this, but invariably have returned to the time-honored repetitive demonstration of the skin eruption in the flesh. While we have not been able to propound any set or routine method of teaching and do not in this inquiry offer such, we are convinced that there is much to be gained from these answers in this questionnaire and that the best instruction is got in the presence of the patient, and we intend in the future to dispense with formal lectures and show fewer lantern slides and diagrams.

COMMENT

We began this inquiry into medical education in dermatology with certain basic premises:

1. There is and has been for some time abundant evidence of general dissatisfaction with the existing teaching programs, and there is need for a critical reevaluation of medical teaching.

2. Owing to the great expansion of medical knowledge in recent years, there is general agreement that no longer can one expect the medical student upon graduation to be an adequate practitioner of medicine.

3. We would limit this critique to undergraduate instruction in dermatology as it occurs in a medical school which is engaged solely in undergraduate teaching.

4. We hoped by this inquiry to find a method of enlarging and improving our undergraduate teaching of dermatology.

In this inquiry we find ourselves confronted with and limited by some inescapable facts:

1. In the face of expanding medical knowledge the medical curriculum has not expanded beyond the same four years' duration of nine months each year. In fact, other activities of students (such as extra laboratory duties, history taking, and part-time intern duty) have shortened the real time available.

2. The medical school has not assumed a responsibility for either graduate or postgraduate instruction and therefore is not sympathetic to the creation of a separate department of dermatology.

3. The teaching of a specialty like dermatology is cramped by the available time of the voluntary instructors, the available time of the student, and the physical space of a community hospital, as well as by lack of finances.

With these premises in mind and contending with these facts, we have presented an outline of our minimal teaching program as it exists, with all its faults and limitations. In addition, we have presented data from 139 physicians to show that in fact they find their instruction in dermatology as undergraduates inadequate to their needs, and that in recognition of this they desire postgraduate instruction in dermatology. Furthermore, they predominantly favor more personal and individual instruction as students and more opportunity to treat and care for patients rather than to be told by lecture or shown by lantern slides, and they are not interested in laboratory or research procedures even when related to the specialty.

It appears, then, that as teachers of cutaneous medicine we are unable to reconcile our ideals and desires with the immutable facts and realities of our position. While we cannot excuse our own faults of instruction, we are unable to conclude that the dermatologist should feel personally responsible for the inadequacy of undergraduate education, since he is only a small part of a large order. Furthermore, there appears to be no necessity for the enlargement of the undergraduate teaching of dermatology, or any object in the equipment of a more elaborate department for the teaching of dermatology to the undergraduate, when there is no room or place for it in the curriculum. The necessities of the times seem to dictate that the teaching of cutaneous medicine must be sublimated to a greater need for deeper instruction in what Gregg¶ so aptly termed "great medicine." We must hold ourselves in hand in order to balance the general medical education. It is quite possible that we are confusing education with intelligence and making too much of teaching and not enough of the art of learning.

From this inquiry we can draw the following conclusions:

1. Undergraduate instruction in dermatology is not, and cannot be, adequate within the limits imposed upon the teaching of medicine by the four-year curriculum.

2. The dermatologist need not feel responsibility for this inadequacy, either because of his method of teaching or his lack of energy in imposing his specialty into an overcrowded curriculum.

¶ References 16 and 17.

3. Dermatologists under these limitations, even with ideal departments, cannot expect to broaden the teaching time in the curriculum. On the contrary, in the future they may have to accept less.

4. As an avowed internist, the dermatologist must find his place in the undergraduate teaching program, as a teacher not of skin diseases as such but as a teacher of cutaneous medicine within the framework of "great medicine."

5. The medical school must eventually assume responsibility for graduate and postgraduate instruction in dermatology (and other specialties) and cease to be wholly satisfied with the production of an M.D. degree. It is in this type of school wherein the teacher of cutaneous medicine can find his greatest usefulness.

ABSTRACT OF DISCUSSION

DR. THOMAS W. MURRELL, Richmond, Va.: To an emeritus professor this paper creates nostalgia, for the problems presented have occurred over and over again in my life for 50 years in the Medical College of Virginia, a school entirely comparable to Emory University. If I were to suggest a literary title, it would be "A Study of Time and Tide."

The Medical College of Virginia, founded in 1836, was a one-year school for 40 years. In the early 80's it became a two-year school, in 1893 a three-year school, and in 1899 a four-year school, which it still is—30 years from one year to four, and 54 years unchanged. Yet in the 54 years subjects which were embryonic have grown into full departments. All the departments are feeling themselves deprived of enough time to do their jobs well, while looming on the horizon are new camels who will try to get their necks into the tent—for instance geriatrics, virology, and atomic energy.

Assuming that there are two fixed quantities in this problem—first, the four-year curriculum and, second, a human being, the medical student, who is being treated to tolerance—time is all that can be modified, and we all shall have to take a cut.

The position of dermatology as a human need is an interesting psychological problem which seems to be based not on what we actually are but what our brothers in medicine think we are. This was well illustrated in World War II. McGuire General Hospital was organized in Richmond and activated at Fort Lee. The dermatologist on the staff asked the Colonel in command for a ward for his patients and was told that it was entirely unnecessary, but he did give him a room in the urological ward. Soon the influx of patients became such a pest to his urological hosts that they protested and larger quarters were given dermatology. When the hospital finished its last assignment in Naples, the dermatological service had grown to one of the large wards of the organization and had received a citation for excellence.

So, who is to define the limits of dermatology in undergraduate teaching? Not the internist, who thinks of living as success and death the only failure. Not the surgeon, who, knowing little of it, therefore concludes there is little to it. Not the pediatrician, who classifies disease on the age of the patient.

The iron curtains are not all in Russia, and the dermatologist must stand on the philosophy of Jefferson, who laid down the principle that the sick man has an *equal* right—to life, liberty, and the pursuit of happiness. If we must clean our own house, the subject is too controversial for one man's opinion to be final. To illustrate, I feel that nothing should be taught the undergraduate which needs a biopsy to confirm the clinician's diagnosis. However, I readily concede that that statement is debatable.

What all schools need is a dean, whom the dermatologist can accept as his attorney. Such a dean would have a wisdom born of a knowledge of human needs, plus an appreciation of the inalienable rights of the student, plus the technique of a sergeant of Marines.

DR. E. J. TROW, Toronto, Canada: I don't wish to prolong the discussion on this very interesting topic, but it is one in which I have been interested for many years and I want to make a few short observations.

The standards of education and examination set up by the Royal College of Physicians and Surgeons in Canada have, in a few short years, greatly improved the quality and character

of teaching of the undergraduate student. This change has come about by virtue of the fact that the younger teachers, before a university appointment is made, are required to pass the examination for fellowship in the Royal College in Medicine, Surgery, or one of the specialties. This fellowship goes beyond certification and demands a thorough grounding in the basic sciences, internal medicine, and general pathology. His instruction to the undergraduate, then, comes from a much broader base, I believe, than is ordinarily found in medical schools, and it may be that this change or this new approach to undergraduate teaching is now desirable.

Dr. G. W. Binkley, Cleveland: I should like to report on the proposed curriculum changes at our school. At Western Reserve School of Medicine we are now at the transitional point at which the standard didactic teaching by lectures will be modified. Our dean, mindful of the great increase in medical information, and recognizing that a good physician is a perennial student, does not plan to produce finished physicians in four years.

We shall discontinue freshman and sophomore, junior and senior categories. There will, of course, be four years, but the curriculum will be composed of Phase 1, Phase *2a*, Phase *2b*, and Phase *3*.

In this program an amazing innovation has occurred. The amount of time the student is in the classroom has been reduced, giving him a day and a half or a day a week of free time for reflection, study, and investigation.

In regard specifically to what will happen to dermatology, it seems that a correlative teaching program is to be developed. A patient will be demonstrated by a group of physicians, including the internist, the pathologist, and the dermatologist. As I said, this is the beginning. We are on the threshold of it. The lectures will go on in this next year, and after 1954 and 1955, we shall be able to report on the new curriculum.

Dr. C. Guy Lane, Boston: As a former teacher and as a participant in the examination of questionnaires which were sent out in the survey back in 1947, I want to congratulate Dr. Alden and Dr. Jones, and I also want to congratulate the program committee for taking this paper. I believe that we should have more papers of this sort and more interest in this subject by the A. D. A. and the Academy. It is a subject which has a long-range influence on patient care. We have diagnosis and treatment of skin diseases in our programs, as we have had previously, but we as a group have a very definite responsibility for the long-range care of patients with skin disturbances.

Let me mention only two phases of this undergraduate teaching program. First, of course, is the opportunity to convey information to undergraduates which should help them later on as physicians to avoid a good many of the mistakes in treatment and diagnosis, as Dr. Alden has mentioned. Secondly, it should also serve to interest undergraduate students in the specialty of dermatology and provide a stimulus, perhaps, which will increase our ranks with good dermatologists later on.

I am delighted that this paper, with the experience of one school in improving dermatologic teaching of undergraduates, has been presented. It serves to emphasize very vividly the relationship of dermatology to the curriculum and a means of improving the instruction. I urge that more papers of this type from other institutions be brought to the attention of the A. D. A. and the Academy.

Dr. Herbert S. Alden, Atlanta: I want to thank you gentlemen very much for your discussion. I wish to say, like Dr. Binkley, that strange things are going to happen in our medical school, too, which, from my own point of view, is a result of our questionnaire. I am completely dissuaded against lectures in dermatology. There will be none of those. The dermatology instruction will begin in the latter part of the freshman year, and we shall have some discussion of dermatology in the sophomore year. In the senior year, there will be no real dermatology teaching, but the student will get it in consultation as best he can. In his senior year, there will be a series of combination clinics and demonstrations at once-a-week intervals.

I want to thank Dr. Lane for his remarks, and I should like to say this, not as a challenge, but as a point of interest: If some of the teachers of dermatology would take such a questionnaire as I have outlined and send it to their graduates, they might be chagrined, as I have been, but quite possibly instructed in the poverty of their dermatological instruction to the undergraduate.

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PITFALLS IN THE DIAGNOSIS AND TREATMENT OF MELANOMA

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IN A REVIEW of the early history of melanoma, Eiselt [1] reported a few records of black tumors described in the late 18th century, shortly after which Laennec [2] identified the disorder, to which he gave the name *la mélanose*, as a rare form of cancer. Dupuytren [3] maintained that he had identified and described the condition in his lectures on pathology before it was reported by Laennec. The designations assigned to the disease by various workers are given in Table 1. The term "melanoma," used almost universally today, was introduced by Carswell in 1838.[4]

TABLE 1.—*Designations for Melanoma*

Laennec [2]	1826	La mélanose
Alibert, quoted by Eiselt [1]	1861	Cancer mélané
Harless, quoted by Eiselt [1]	1861	Melanosis pseudoplastica, tuberculoides, saeculata
Jurine, quoted by Eiselt [1]	1861	Cancer anthracine
Breschet [74]	1821	Dégénérescence noire
Sundelin [75]	1827	Carcinoma melanoides
von Ritgen [76]	1828	Melanomyces; Schwarzschwamm; Pigmentschwamm
Carswell [4]	1838	Melanoma
Walther and others [77]	1839	Fungus hematodes; cancer melanoides
Schoenlein [78]	1841	Venenkrebs; carcinome der vene
Vogel [79]	1847	Melanotic tumors (Pigmentkrebs)
Virchow [80]	1847	Melanotische Krebs
Paget [81]	1863	Melanotic cancer; melanoid cancer
Kaposi [82]	1895	Melanosarcoma
Unna [31]	1896	Nevocarcinoma
Lubarsch [83]	1925	Melanocytoblastoma

Driver and MacVicar [5]; Webster, Stevenson, and Stout,[6] and many others have emphasized the difficulties in the clinical diagnosis of melanoma. Allen [7] reported that 218 specimens of melanoma had been received in the Army Pathological Department during World War II. He emphasized the fact that clinical diagnosis had not been accurate, that many benign lesions had been called malignant and vice versa.

However, little statistical evidence is available. Swerdlow [8] reported that of 57 specimens diagnosed as melanoma clinically, only 16 (28%) were corroborated by biopsy. Of 27 melanomas diagnosed microscopically, only 59% had been diagnosed clinically. At the University of Chicago Dermatological Laboratory, from Oct. 1, 1927, to March 27, 1953, clinical and/or laboratory diagnosis of melanoma was made on 244 specimens. Of 169 specimens on which clinical diagnosis of melanoma had been made by dermatologists and graduate students in dermatology, micro-

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Read at the Seventy-Third Annual Meeting of the American Dermatological Association, Lake Placid, N. Y., June 13, 1953.

scopic confirmation was made in 72 (43%), as shown in Table 2. Of 151 specimens on which microscopic diagnosis of melanoma was made, clinical diagnosis had been made in 72 (48%), as shown in Table 3. It is noted that pigmented nevus occupies the second position in Tables 2 and 3. However, twice as many were diagnosed clinically as microscopically. It seems that physicians make a diagnosis of pigmented nevus too readily, thus closing their minds to the possibility of melanoma.

Poor as this average is for pigmented melanoma, that for the nonpigmented variety is even worse. It is practically never diagnosed clinically, to which attention was directed by Horwitz.[9] Diagnoses are usually granuloma pyogenicum, carcinoma, or verruca. The various designations given to nonpigmented melanoma are leuco-

TABLE 2.—*Laboratory Diagnosis in 169 Cases Diagnosed as Melanoma Clinically*

Melanoma	72 (43%)
Nevus pigmentosus	18
Blue nevus	14
Melanotic carcinoma	10
Lentigo	10
Seborrheic keratosis	7
Thrombosed angioma	5
Verruca vulgaris	5
Angiofibroma with hemorrhage	3
Metastatic melanoma, squamous cell carcinoma, senile keratosis, tattoo, dermatitis, nevus and blue nevus	2 each
Bowen's disease, mixed tumor of parotid gland, blood cyst with thrombosis, neurofibroma with hemorrhage, acquired nevus pigmentosus, Kaposi's sarcoma, carcinoma with hemorrhage, lupus vulgaris, chronic inflammation with melanosis, adenoma sebaceum, mucous cyst, granuloma pyogenicum, nonspecific ulcer	1 each

TABLE 3.—*Clinical Diagnosis in 151 Cases of Melanoma Verified Microscopically*

Melanoma	72 (48%)
Nevus pigmentosus	36
Seborrheic keratosis	7
Granuloma pyogenicum	7
Carcinoma	5
Melanotic carcinoma	4
Lentigo	4
Fibroma	3
Thrombosed angioma	2
Sebaceous cyst	2
Angiokeratoma, angiofibroma with hemorrhage, mixed tumor of parotid gland, blue nevus, Kaposi's sarcoma, sarcoid, tumor, leucoderma acquisitum centrifugum, melanosis	1 each

sarcoma (Borst [10]), amelanosarcoma or amelanoma (Deelman [11]), nonmelanotic melanoepithelioma (Horwitz [9]), amelanotic melanoma (Miescher [12]), and nevocytoblastoma or malignant nevocytoma (Symeonidis [13]).

Pack and Adair [14] listed the following disorders to be distinguished from melanotic whitlow:

1. Paronychia, whitlow (felon), osteomyelitis
2. Pyogenic granuloma
3. Onychomycosis nigricans
4. Subungual hematoma
5. Primary syphilis
6. Gangrene of toe
7. Dupuytren's exostosis
8. Subungual fibroma
9. Subungual keratosis
10. Subungual carcinoma
11. Subungual Kaposi's sarcoma
12. Glomus tumor
13. Metastatic tumors of nail bed

To this list should be added subungual larva, called to my attention by Dr. Leo Zimmerman, whose patient had contracted the disorder in Central America. Other conditions to be differentiated are syphilitic dactylitis and myeloma, as reported by Fordyce.[15]

Symeonidis [13] recommended the dopa reaction as a positive diagnosis of melanoma. Such a reaction was reported by Bloch,[16] Miescher,[17] Becker,[18] and others. Fitzpatrick [19] found a positive tyrosine reaction in seven human amelanotic melanomas and weakly positive reactions in junctional nevi. The tyrosine reaction has the advantage of specificity, but Allen and Spitz [20] believe that other methods of diagnosis are more important and practical at the present time.

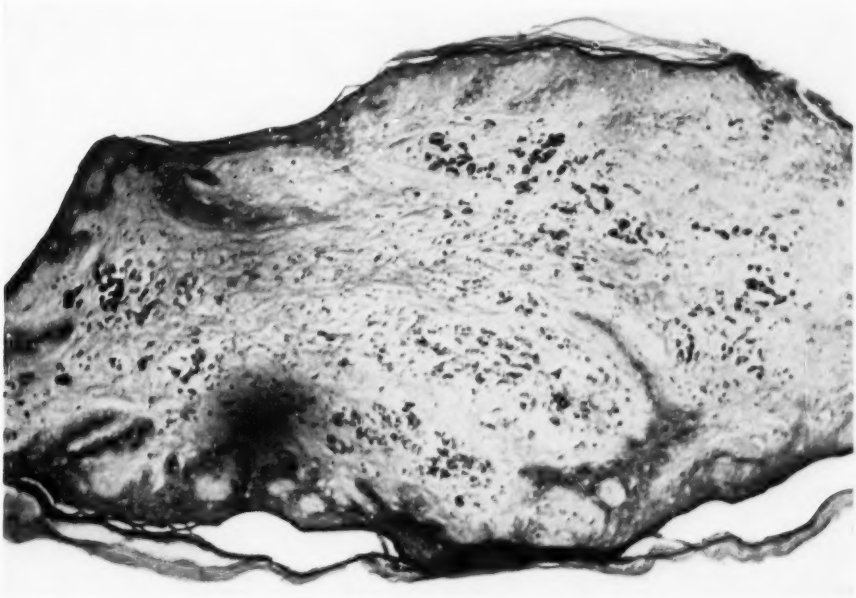

Fig. 1.—Subcutaneous black tumor possibly resulting from implantation of tissue by a sliver. The epithelium is hyperpigmented, and the connective tissue contains many melanin-filled chromatophores. Low power; silver nitrate reaction; methyl green counterstain.

Goldman [21] introduced a new method of diagnosis in the form of gross cutaneous microscopy. He studied nevi, junctional nevi, and melanoma. A nonpigmented melanoma gave the impression of dirty granulation tissue.

The following case report illustrates an unusual variety of pseudomelanoma which I recently observed.

CASE 1.—A man aged 50, a woodworker, had had a bluish semimovable subcutaneous tumor on the extensor surface of the right ring finger for two or three years. He often got slivers in his hand but did not remember having had one in this location. The gross tumor was black. Microscopic examination revealed a subcutaneous tumor covered with epithelioma, which was deeply pigmented with melanin (Fig. 1). Diagnosis was made of benign tumor, presumably formed from tissue which had been penetrated with a sliver.

Another section of an interesting pigmented lesion was seen through the courtesy of Dr. F. T. Becker, of Duluth. The clinical impression had been that of blue nevus. Microscopic examination revealed pigmented benign adnexal epithelioma (Fig. 2).

Other conditions to be differentiated from melanoma of the oral cavity are various hemorrhagic and pigmentary disorders, due to deposition of melanin,

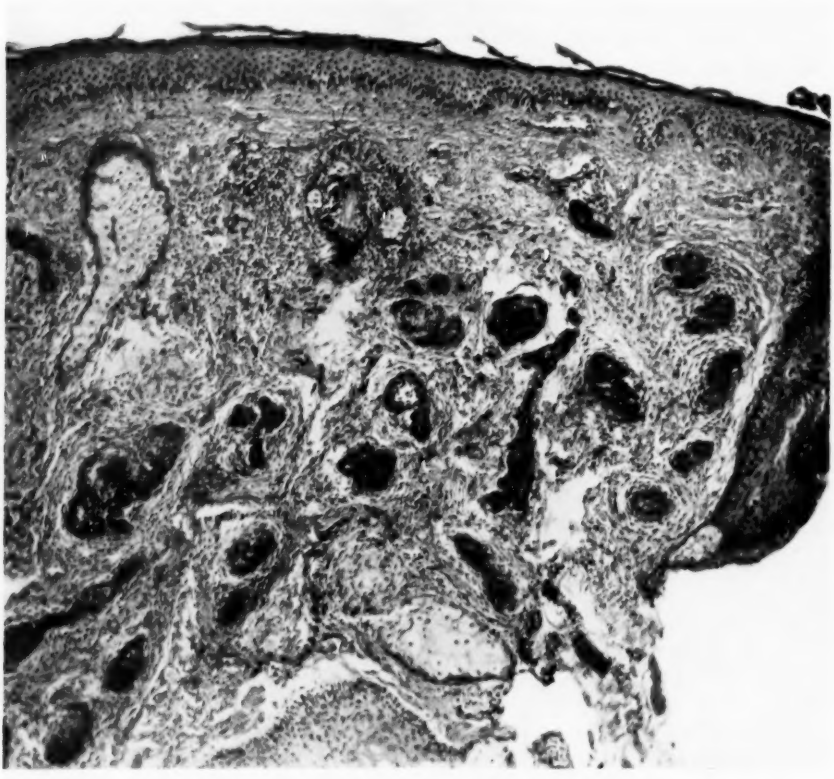

Fig. 2.—Pigmented benign adnexal epithelioma. The black areas are melanin. Low power; hematoxylin and eosin (courtesy Dr. F. T. Becker).

bismuth, lead, or mercury. New and Hansel [22] reported finding a piece of pencil lead in a tumor which was suspected of being melanomatous.

COURSE OF MELANOMA

It is usually reported that cutaneous melanoma spreads early via the lymphatics, rather than the blood stream, although the latter route has been emphasized by Scharnagel [23] and Lund.* Handley [24] showed that, while melanoma spreads super-

* Lund, H. Z.: Personal communication to the author.

ficially in the form of satellite lesions, the extent of spread in the lymphatics in the deep fascia over the muscles is much greater, a point of considerable importance in treatment. After a certain time, perhaps depending on the degree of anaplasia of the primary tumor, the regional lymph nodes are involved. According to Raven,[25] 50% of lymph nodes involved in metastatic growth are not palpably enlarged. From the lymph nodes, the tumor eventually invades the blood stream. According to Willis,[26] no tumor takes up its abode so easily in all tissues as does melanoma; hence it may be found in any part of the body. After involvement of internal organs, especially the liver, melanuria, studied by Rothman,[27] and, more rarely, generalized tissue melanosis, as reported by Odel, Montgomery, and Horton,[28] may occur. There have been about 20 reports of such melanosis in the literature.

PATHOGENESIS

Melanoma arises as malignant neoplasia of melanoblasts or melanosytes[29] at the epidermodermal junction of the cutaneous surface or the junction of the epithelium and the tunica propria of the mucocutaneous junctions or mucosae.[30] In some instances the tumor arises in a pigmented nevus. Statistics relative to the percentage of origin in nevi vary from 100%, claimed by Unna[31] and Nicholson,[32] for pigmented melanoma, nearly 100% by Willis[33] and Ewing,[34] down to 25%, by Miescher,[17] 20% by Williams and Martin,[35] and 18% by Daland and Holmes.[36] Pack[37] showed that the distribution of nevi and melanomas are not the same. Few nevi are seen about the genitalia and feet, but melanomas are more abundant in those regions. Nevi are almost unknown on the mucocutaneous junctions and mucosae, but melanoma occurs there in some instances.

Many workers recognized that only a small percentage of melanomas arose in congenital nevi which had been present since infancy and that most of them arose as, or in, brown plaques which had been present for a few months or years. Hutchinson[38] was the first to emphasize this point, and he called the brown plaque "melanotic freckle" or "melanotic infective freckle" to emphasize its tendency to enlarge. This diagnosis was purely clinical, and microscopically three different pictures were seen: (1) simple lentigo, (2) pigmented basal-cell carcinoma, and (3) lentigo maligna, leading to melanoma. It should be mentioned that some of the early reported pigmented carcinomas of the skin were probably melanomas. Hartzell[39] stated in 1903, "In this connection, it may be observed that a considerable number of so-called pigmented nevi which become carcinomatous are in fact not congenital growths (if the statements of patients are to be believed) but have appeared some time after birth. In such cases it is often difficult, if not impossible, to determine whether or not the growth was cancerous from the beginning." Dubreuilh[40] translated Hutchinson's "malignant freckle" into French as *lentigo malin du vieillard* but later used the term *mélanose circonscrite précancereuse*.[41] Hazen[42] called the brown spot an "acquired mole"; Deckner[43] and Kumer and Lang,[44] *tardive nevus;* Brown and Byars,[45] "developmental mole"; Traub,[46] "junction type mole"; Sachs and co-workers,[47] "junction nevus," and Allen,[7] "dermoepidermal nevus." My own preference is "lentigo maligna," "lentigo" meaning an acquired brown macule and "maligna" denoting the ominous nature of the process. I believe that lentigo maligna is an obligative premalignant (or malignant) lesion,

an opinion shared by Reese [48] for conjunctival melanosis. It is necessary to distinguish lentigo maligna from an acquired nevus, which is a benign lesion. Miescher [12] gives the following points of differentiation:

1. The size of the macule

2. Progressive change, not only in growth but also in regression (Changeability is characteristic of precancerous melanosis, as against the stability of a nevus)

3. The frequent grouping of several spots by apposition of new elements

4. Chronic plasma cell inflammation and the atrophy

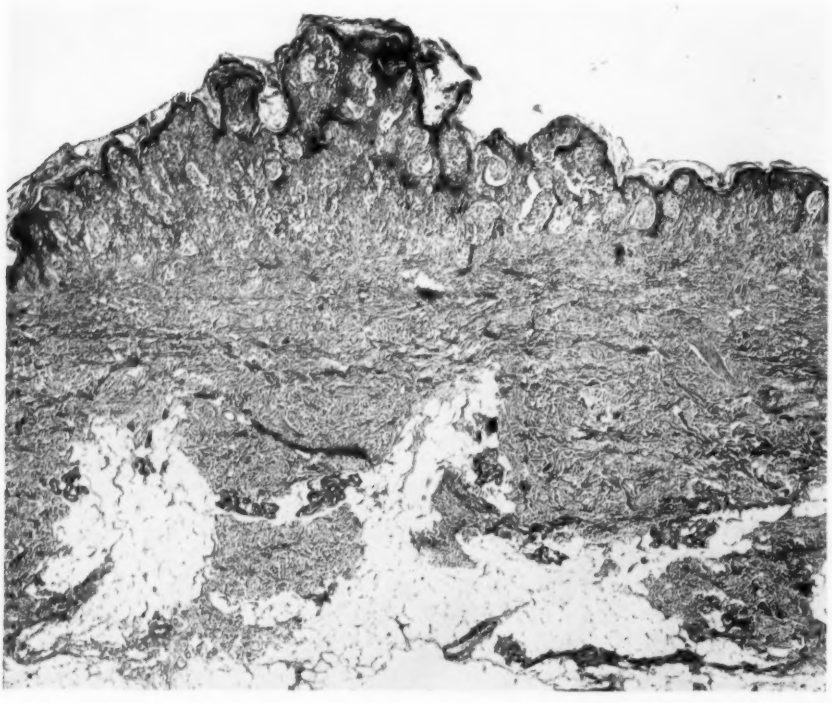

Fig. 3.—Lenigo maligna of three years' duration. Low power; hematoxylin and eosin (courtesy Dr. W. W. Wilson).

5. The eminent disposition to melanoma formation

The following case illustrates lentigo maligna, possibly aggravated by pregnancy and trauma, presented through the courtesy of Dr. W. W. Wilson, of Tampa, Fla.

CASE 2.—A woman, aged 22, was seen in the eighth month of pregnancy. She had had a brown lesion above the elbow of the right arm for about three years. It had always had a millet-sized elevation in the center. It had not changed in size, shape, or color, but she had injured it three months previously by scraping it against a wire. The clinically dark-brown plaque, 5.0 by 7.5 mm., suggested a pigmented nevus with a verrucous nonpigmented lesion in the center. Because of the possibility of melanoma, the plaque was excised. There was no clinical evidence of local extension.

Microscopic examination revealed a gradual change from the border to the center of the lesion (Fig. 3). The periphery was hyperpigmented, and melanocytes were larger than normal, without actual increase in number. Toward the center, multiplication of anaplastic cells resembling melanocytes had occurred, with extension of the masses toward the cutaneous surface. At the center, large masses of anaplastic cells were present just beneath the thinned stratum corneum and also extended into the dermis. Moderate lymphocytic infiltrate was seen in the dermis. No nevus cells were evident. Diagnosis of lentigo maligna was made. A similar picture was reported by Becker [18] in a nevus.

A history of a preexisting brown lesion present since childhood is presumptive evidence that a melanoma has originated in a congenital nevus, but irrefutable evidence would be the finding of nevus cells in a tumor which is obviously melanomatous. Such evidence could be obtained with certainty only by serial sectioning, which is not feasible. Evidence in our laboratory is that signs of preexisting pigmented nevus is seen in only about 23% of tumors. It is evident, therefore, that numerically most melanomas do not originate in pigmented nevi. However, when the surface area of the normal skin is estimated at 16,000 sq. cm.[49] and the surface area of the 10 to 30 nevi possessed by the average person is usually much less than 100 sq. cm., it is evident that melanoma occurs in nevi relatively more frequently than in normal skin. It has long been my impression that melanocytes are more prominent in many nevi than in normal skin.

There is no evidence that melanoma cells arise from nevus cells, although such origin has been maintained by Lipschütz,[50] Ewing,[34] Dawson,[51] Willis,[33] and Kreibich,[52] who stated that melanoblasts form melanosarcoma and that nevus cells form alveolar sarcoma. This is probably erroneous, because it is a general pathological principle that malignant cells do not arise from benignly neoplastic cells, but rather de novo.

PATHOLOGY

The color of the gross tumors which have arisen in lentigo maligna or a pigmented nevus vary from erythematous in the nonpigmented or slightly pigmented tumors through various shades of brown to black. The tumors are characterized by their relative fragility, with bleeding on injury. I am inclined to believe that injuries to pigmented nevi which are alleged to have encouraged the production of melanoma have, in most instances, occurred after malignancy has supervened, rather than before. The type of nevus which is most apt to give rise to melanoma is the smooth brown one and not the blue-black or the slate gray lesions, which are already malignant. The smooth brown nevi are the type A or AB [53] with nevus cells at the epidermodermal junction.

HISTOPATHOLOGY

Boyd [54] stated, "The microscopic evidence of the malignant transformation of a nevus is usually readily recognized, but sometimes presents great difficulty." Inception of melanoma as lentigo maligna or in a pigmented nevus is characterized microscopically as follows:

(*a*) Cells, either fusiform or oval, with nuclei and cytoplasm larger than those of normal melanocytes or nevus cells. Mitotic figures are seen only rarely before the tumor stage is reached. These cells appear singly or in groups at the epidermodermal junction, from which location they extend in two directions: outward

through the epidermis, to be cast off in the stratum corneum, and inward into the dermis. The outward extension, to which attention was called by Waelsch [55] and by Darier,[56] is practically never seen in nevi and is one of the earliest earmarks of malignancy.

(*b*) Lymphocytic, and sometimes plasma cell, infiltrate, often quite abundant in early lesions, is located in the papillae and superficial dermis. After the melanoma has advanced to the tumor stage, the infiltrate may be less pronounced. Such an infiltrate is seen in benign nevi only when they have become infected or in seborrheic persons, where the infiltrate is usually very scanty.

The only difference between melanoma arising as lentigo maligna and that arising in a nevus is the presence of nevus cells in the latter.

JUVENILE MELANOMA

A type of tumor which I had always considered as a special variety of childhood nevus was presented by Spitz [57] as juvenile melanoma, which differs from the adult variety by the presence of fusiform or oval cells lacking cohesiveness, usually nonpigmented; failure of such cells to work their way to the surface (this feature was not mentioned by Spitz); presence of giant cells, and failure to metastasize. Local recurrence, with the clinical picture of juvenile melanoma, took place in one patient, from whom a specimen was taken and examined.

TREATMENT OF MELANOMA

The current treatment of early melanoma is surgical. Roentgen and radium therapy had some advocates for a while, but Stewart [58] showed that only 2% of melanomas are radiosensitive, and it was abandoned by Pack and co-workers [59] as being completely ineffective, since they had had no five-year survivals after its use. Ellis [60] reported that 53 patients with melanoma, including that of the eye, had been treated at the Sheffield Radium Center and that no patient with histologically proved melanoma had survived. Driver and MacVicar [5] failed to influence metastatic lesions with irradiation. Radioactive phosphorus and arsenic have been tried, without result. It is too much to expect that any radioactive isotope will be much better than other forms of radiation, since the tumor cells are radioresistant.

Because of lymphatic extension in the deep fascia far beyond clinically visible superficial spread, as demonstrated by Handley,[24] a large area should be removed with the primary lesion. The best permanent results have followed removal of the primary tumor, lymphatic channels, and regional lymph nodes *en bloc*. Soon after this method was recommended for treatment of mammary carcinoma independently by Willy Meyer and by Halsted,[61] in 1894, Pringle,[62] in 1898, applied it to removal of melanoma of the arm, and for melanoma of the thigh. Metastases were found in regional lymph nodes in Pringle's two patients, who were demonstrated 38 and 30 years later, respectively,[63] to have no history of recurrence. This method is most easily applied to melanoma on the extremities or face and least readily to lesions on the thorax and abdomen because of the inaccessibility of lymph channels and regional nodes. Handley [64] recommended the *en bloc* dissection where feasible. Raven [25] excises the primary lesion widely and deeply, then removes the regional lymph nodes after 10 to 14 days. De Morgan [65] stated in 1872, "Today, the glands

may be free; tomorrow, they may be affected. Today, the disease may be within the range of an operation; tomorrow, disease may be distributed far beyond." Hence, it seems to me that the sooner the lymph nodes are removed the better. Williams [60] believes that operation for melanoma is so urgent that he calls it a surgical emergency. If metastases are found in the inguinal or axillary nodes, Pack [37] sometimes performs amputations.

Surgical treatment of late melanoma is predicated on failure to demonstrate systemic metastases.

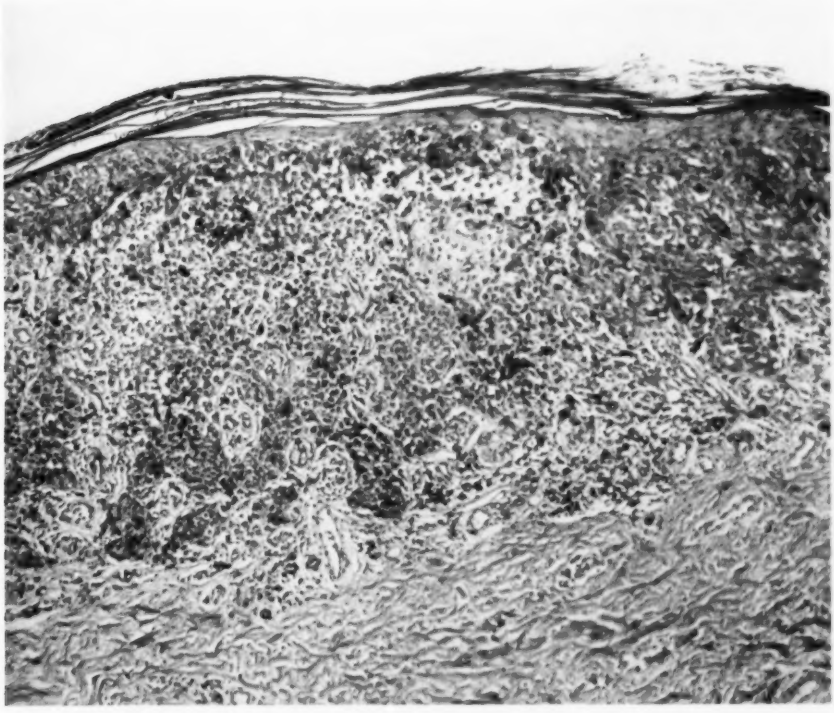

Fig. 4.—Lentigo maligna with early tumor formation. Low power; hematoxylin and eosin.

The following three patients were treated by wide and deep excision of early melanoma, with resection of the regional lymph nodes.

Case 3.—A woman, aged 33 had always had a "mole" on the median plantar surface of the right foot. Within the last year she had noted scaling around it, and serum had exuded. During the last month it had become elevated. A specimen for biopsy sent by Dr. Harold Tannenholz, showed nonpigmented melanoma. The local area was removed widely and deeply, and a strip of tissue was removed up to and including the femoral and inguinal nodes. She reported nine years later that there had been no recurrence.

Case 4.—A woman aged 52, referred by Dr. R. S. Starkweather, had had her attention called 10 years previously to a brown macule on the posterior mesial aspect of the right leg 14 cm. below the calf. She believed it had remained the same size, but the lower portion of the plaque

had become elevated and was a little tender. She presented a dark-brown plaque 7.5 by 15 mm., the lower one-half of which was slightly elevated. A biopsy specimen of the lower portion (Fig. 4) showed malignant neoplasia of melanoblasts at the epidermodermal junction, with extension to the surface and slight penetration into the dermis. Moderate round-cell infiltration was present in the superficial dermis, with a moderate amount of melanin in chromatophores. Dr. John Prohaska performed an operation consisting of a radical dissection of the right inguinal nodes, and a strip of skin at least 5.0 cm. wide, subcutaneous tissue, and the vena saphena magna was excised *en bloc* from the groin to the mesial malleolus to include the primary lesion. No evidence of melanoma was found by microscopic examination in the primary site or the lymph nodes.

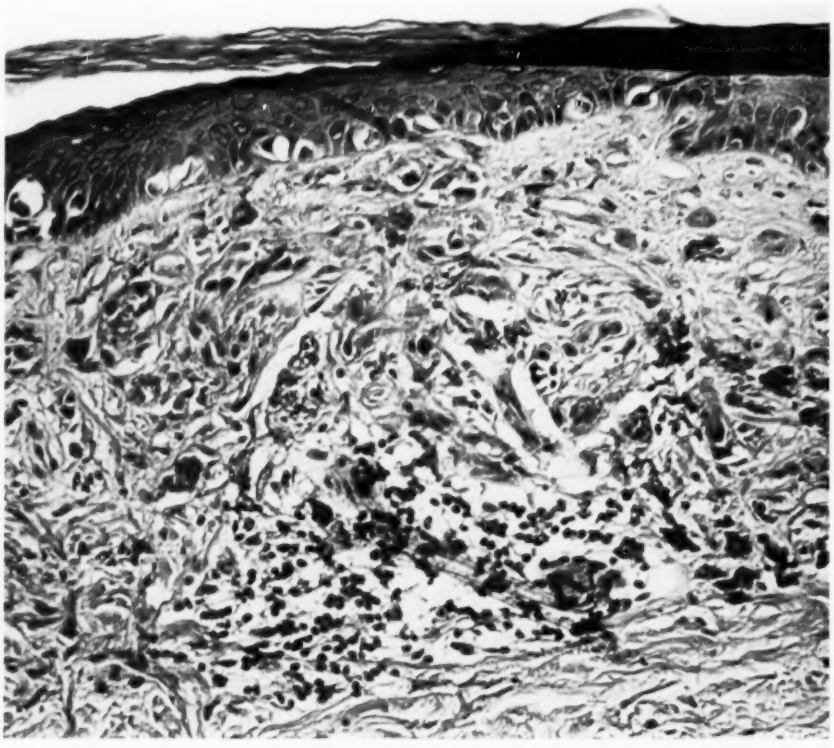

Fig. 5.—Early lentigo maligna. Multiplication of melanocytes at epidermodermal junction and round-cell reaction in dermis. High power; hematoxylin and eosin.

Case 5.—A woman aged 56 had noted a brown spot on her left leg for five years, which had been enlarging for the past few months. She presented a dark-brown lesion 4.0 by 7.0 mm. in size on the median surface of the left leg. Microscopic examination (Fig. 5) showed anaplastic melanoblastic cells, some of which appeared in nests in the epidermis, some singly in the epidermis, and some singly in the dermis. Only a few cells had worked their way through to the surface. In the areas of activity there was perivascular lymphocytic inflammation. Diagnosis of lentigo maligna was made, and an operation was performed by Dr. John Prohaska. The regional lymph nodes were resected, and a large area, including the primary lesion, was excised deeply. On microscopic examination no metastases were found in the lymph nodes.

I should like to present a progress report on a patient discussed previously.[55] A girl, aged 16, had an early melanoma with beginning tumor formation beneath her right shoulder strap. At the age of 23 years, while pregnant, she developed a subcutaneous tumor near one of the ribs on the left lower part of the chest. Biopsy revealed pigmented and nonpigmented melanoma. Caesarean section was performed at eight months to remove the stimulus of pregnancy, and she was advised against further pregnancies. Two years have passed, and she has had no further signs of the disorder.

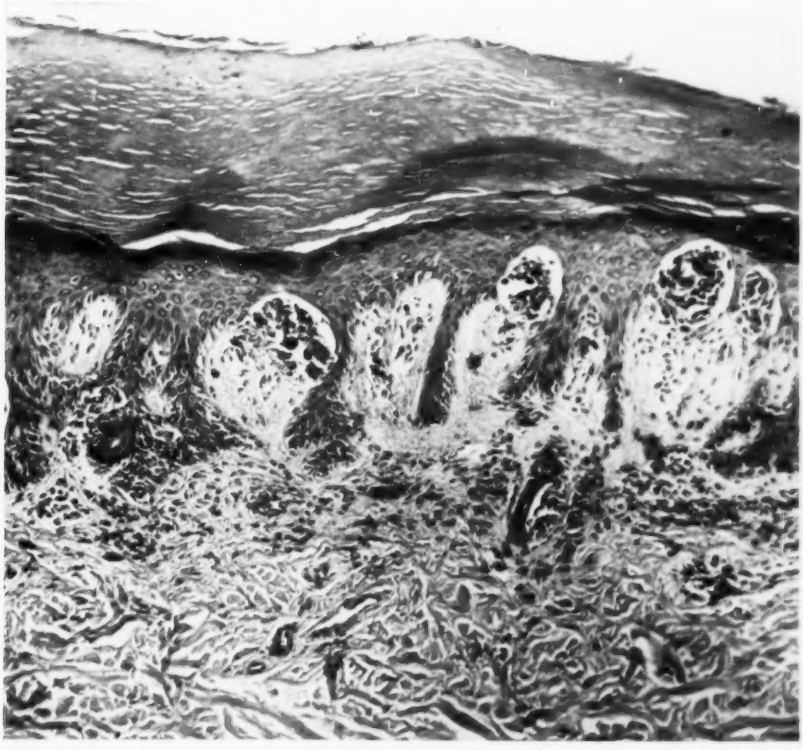

Fig. 6.—Smooth brown (so-called junction) nevus present since childhood on sole of girl, aged 28. No sign of malignancy is seen. Low power; hematoxylin and eosin.

PROGNOSIS

In spite of an adequate working knowledge of the life history of melanoma, the chances for recovery of patients with the disorder are not good. There are several reasons for this discrepancy.

1. The patient is not seen early in the course of the disease. Clark and Macdonald[60] reported that in a Connecticut series of 349 patients, 48.8% of the males and 37.9% of the females had metastases when first seen. In a Texas series of 298 patients, 63.8% of the males and 60.6% of the females had metastases when first

seen. One reason for failure to consult the physician early is the asymptomatic nature of the disease. The current anticancer drives by the American Cancer Society and other organizations have brought more patients to physicians' offices for study of asymptomatic brown spots.

2. The physician does not take a specimen of the lesion for biopsy. Laboratory facilities are available, and biopsy of all pigmented cutaneous lesions should be made.

3. After the diagnosis of melanoma has been made, treatment has not been sufficiently radical. It is not safe to await appearance of satellite lesions and enlarged lymph nodes before removing the involved areas.

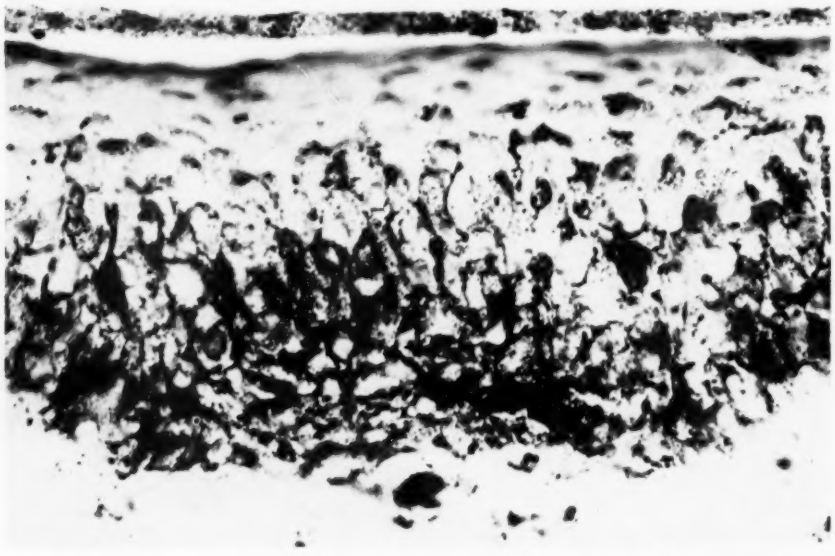

Fig. 7.—Recurrent lentigo from cheek of woman, aged 70, three years after previous treatment. Melanocytic activity, with intense pigmentation but no sign of malignancy. High power; silver nitrate reaction.

4. The actual percentage of cures has improved over the early reports, in which most patients already had metastases, and hence had a poor chance for survival, and is constantly improving. Driver and MacVicar [5] reported that 19 of 35 patients (56.7%) were alive for 7 to 18 years without recurrence. Thirty-one of the 35 had had no clinical metastases. Pack and co-workers [67] reported constant improvement in results. While a five-year cure is not as significant for melanoma as for carcinoma, it is at least a milestone to be used. He reported 39.9% of five-year cures in patients who had not had a previous operation within one month and 17.0% for patients who had had local excision more than one month prior to definitive surgery. He reported 31.2% of five-year cures after amputation.

COMMENT

It is obvious from the less than 50% diagnostic accuracy that clinical diagnosis of melanoma cannot be relied upon. Biopsies must be made of all brown lesions. As has been stated by Bloch,† Kreibich,[52] and Becker,[18] the smooth brown nevus, therefore the type A or AB nevus (Fig. 6), with nevus cells at the epidermodermal junction, is the one most apt to develop melanoma. An opinion is abroad that a person with such a nevus is in imminent danger, which is far from the truth. It is the person with lentigo maligna, which also originates at the epidermodermal

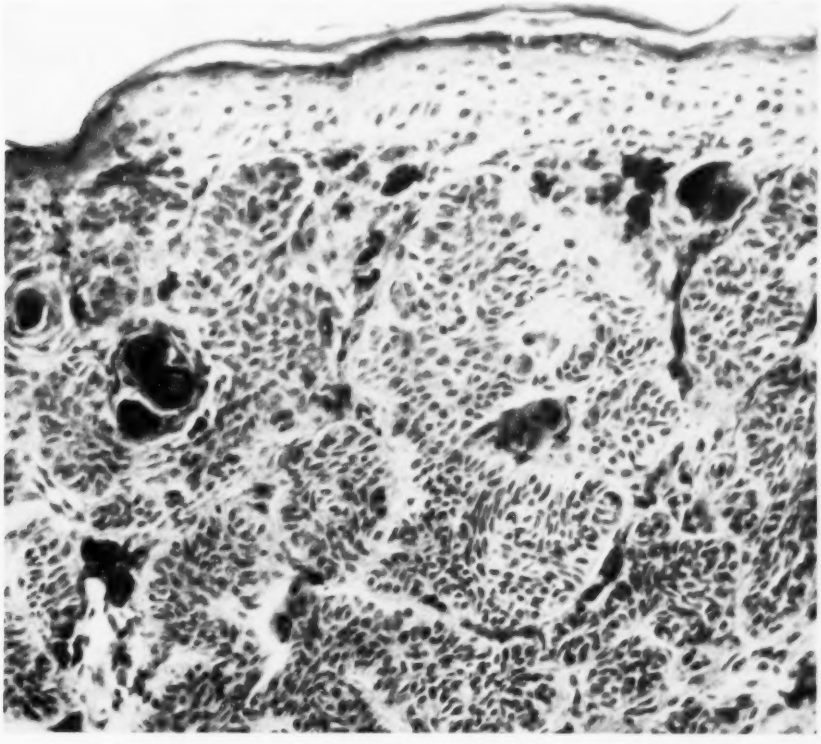

Fig. 8.—Pigmented basal-celled carcinoma. The black areas are melanin. High power; hematoxylin and eosin.

junction, who is in danger, because the lesion is founded on a different type of cell than is a nevus, malignant rather than benign. The malignantly anaplastic cells differ from nevus cells by the higher degree of anaplasia and by their being cast off at the cutaneous surface, as well as penetrating into the dermis. In lentigo maligna a slight to pronounced lymphocytic infiltrate is seen in the superficial dermis. This infiltrate is seen in nevi only when they are infected, or in mild degree in seborrheic persons. These characteristics signify early malignancy, often for years before extension takes place. According to DeMorgan,[69] when a gross

† Bloch, B.: Personal communication to the author.

tumor forms in lentigo maligna, dissemination quickly follows. In my opinion, tumor is a late manifestation, and the physician has ample time for diagnosis and treatment for months or years before such an event.

Black tumors give great trouble in diagnosis. They are seborrheic keratoses, considered elsewhere [69]; lentigo (Fig. 7); pigmented basal-cell carcinoma [70] (Fig. 8), and irritated blue nevi (Fig. 9). My success in clinical differentiation has not been too good, and biopsy is essential.

Adequate surgical treatment is available. However, Ewing [70] stated, "Many surgeons who do not hesitate to carry out radical mastectomies or resection of the stomach or bowel are loath to apply the same radical treatment to melanomas, yet they are dealing with a more aggressive type of neoplasm." Price and co-workers [72]

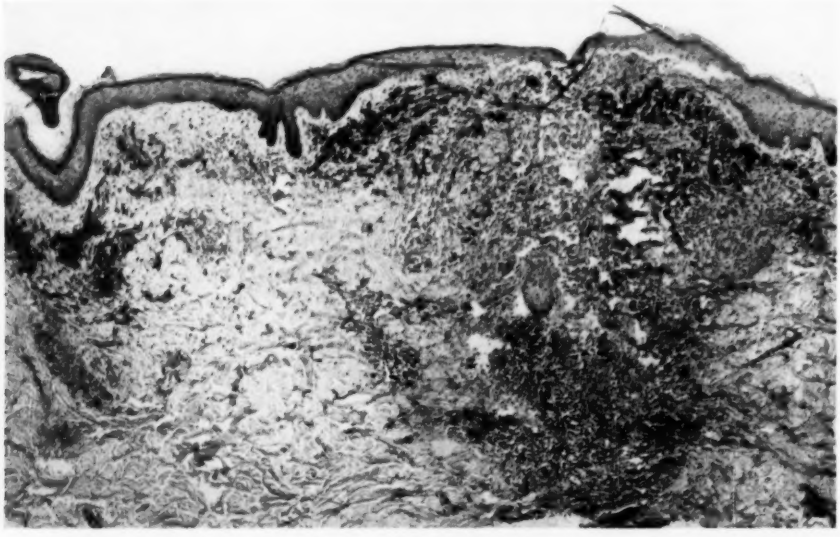

Fig. 9.—Blue nevus with nonspecific follicular and perifollicular inflammation. Low power; hematoxylin and eosin.

stated that it is difficult to convince patients of the need for radical surgery for such an apparently trivial disorder. In most instances in my experience, the patient, who is ordinarily in excellent physical condition, is willing to undergo necessary surgery, which, after all, is not as discomforting or as serious as many other surgical procedures, such as intra-abdominal or intrathoracic operations.

Norman Paul,[73] in his small book "Cutaneous Neoplasms," quoted from Sir James Barrie's play, "The Will": "always in me, a black spot not so big as a pinhead but wanting to spread and destroy me in the fullness of time, all the rest of me as sound as a bell." Not quite anatomically correct, but a timely warning to physicians.

SUMMARY

The history of the study of melanoma and its various designations are reviewed. The course of the disease is presented.

Diagnosis is made clinically in less than half the cases. Biopsy is essential, easy, and safe.

Melanoma originates in pigmented nevi in 25% of instances. It originates as lentigo maligna in 75% of cases.

Treatment of melanoma is surgical and should include lymph node resection.

Prognosis is not good, because (*a*) patients do not consult physicians early, (*b*) physicians do not take biopsy specimens from all pigmented lesions, (*c*) treatment is not sufficiently radical. Prognosis has been improved by earlier and better surgical treatment.

ABSTRACT OF DISCUSSION

DR. JAMES R. DRIVER, Cleveland: Precancerous pigmented lesions of the skin include malignant lentigo, junction nevus, compound nevi, and pigmented nevi, in this order of importance. They are present on the skin of nearly every person in varying numbers, and some persons may have as many as several hundred. Yet, it has been estimated that melanoma is likely to develop in only about one out of every million people. It should be emphasized, however, that a malignant tumor is much more likely to occur in the acquired malignant lentigo.

I find it frequently very difficult to differentiate clinically between a malignant lentigo and a junction nevus. I believe this is true for all of us. It was shown by the author that various writers incriminate the junction nevus as the precursor lesion in from 100% down to 18% of cases. Dr. Becker, basing his opinion upon histologic evidence, finds only 25% of melanomas originating in the junction-type nevus and 75% from the acquired malignant lentigo.

Obviously, it is neither necessary nor practical to remove all pigmented lesions from the skin of every person and have a laboratory diagnosis for each one. The author advises a laboratory diagnosis of all pigmented lesions. I agree that this is desirable for all lesions removed, no matter for what reason. Nevertheless, this could become a laborious and expensive procedure when a large number of lesions are removed from a single patient. However, it is very important that biopsies be done on those precancerous lesions of malignant lentigo or junction nevi which are prophylactically removed from areas that are likely to be subjected to trauma. Such areas include the feet, legs, hands, forearms, area about the waist, breasts, neck, face, ears, scalp, and genitalia.

The author reports in this paper that the clinical diagnosis of melanoma was correct in only 43% in a series of 169 cases. Here we see why a laboratory diagnosis is so important. Yet there are frequently examples of a laboratory diagnosis of melanoma in which the lesion was later shown to be a benign one. Lund found 28 mistakes in a review of 300 cases diagnosed histologically as melanoma at the University Hospitals in Cleveland. Errors in diagnosis were chiefly blue nevi, histiocytoma, and pigmented nevus.

This type of error may be as high as 10% in the best laboratories. Such mistakes become extremely serious if they result in unnecessary amputations or other radical surgical procedures. The laboratory diagnosis of melanoma is of such great importance that it should not become the responsibility of one pathologist.

The prophylactic removal of precursor lesions and the early diagnosis and adequate surgical treatment of melanomas are necessary if we hope to reduce the high mortality of this disease.

In 1943, Dr. MacVicar and I reported a series of 35 patients with laboratory-diagnosed melanomas seen in dermatological practice. Only three had metastasis when first seen. Seventeen, or 48.6%, were alive and well for 7 to 18 years. Nine patients in the series had been treated for less than five years but were living, with no clinical evidence of relapse. These were not evaluated. From this and subsequent experience we believe that in the cases seen by the dermatologist the cure rate could be 50% or better.

Adequate treatment is imperative, but it is here that much controversy occurs. I am of the belief that in many instances in which a clinically benign pigmented lesion has been prophylactically removed and found by laboratory examination that early beginning melanoma has developed, it is sufficient to go back and do only a more extensive local removal of the area.

Prophylactic removal with only a small border of normal tissue is wrong, if an obviously small lesion is clinically suspicious because of increase in size, change in color, or thickness. The lesion should be widely and deeply excised, and, if the laboratory diagnosis is melanoma,

lymph node removal with the intervening lymphatics in continuity should be performed where possible. Melanomas on the extremities in most instances require amputation and removal of the nodes.

We are frequently confronted with the difficulty of getting the consent of the patient to submit to some of the more radical forms of treatment. A cancer surgeon is the one to perform such operations. General surgeons often refuse to do them. Individual evaluation is necessary in every case in determining the type of treatment.

I want to thank Dr. Becker for presenting to us this excellent and important paper. I hope he continues his interest in this phase of the cancer problem.

Dr. Herman Beerman, Philadelphia: As usual, Dr. Becker has given an instructive and most important paper, and I am rather reluctant to discuss it. However, being a purist of the first rank, I should like to decry against the use of the term "melanoma" when we mean "malignant melanoma." This has got to be such a slang expression that when one speaks about other melanotic lesions it is necessary to use another term, "pseudomelanoma," in the sense that it is not malignant melanoma. Actually, these other melanin-containing lesions are really melanomas.

I should also like to ask how often one sees spindle-shaped cells in malignant melanomas, and also what is meant by the term "melanotic carcinoma."

Dr. George C. Andrews, New York: I should like to ask Dr. Becker whether he would tell us clinically how he distinguishes lentigo malignans from junction-type nevus. "Lentigo malignans" is a term which has been tossed about in the literature and has meant a great many different things. I should like to know more about his interpretation of it.

Dr. Earl D. Osborne, Buffalo: I should like to make two points regarding this subject.

Dr. Becker referred to what he thought was a rather slow spread of the malignancy. I took it to mean that he meant from microscopically. He felt that there was a considerable interval of time between the actual onset of malignant development and the widespread lymphogenous spread of the disease. However, I should like to call attention to a survey which we made two or three years ago of approximately 100 cases of malignant melanoma that were carefully studied and followed, and there is a vast divergence between microscopic spread and what the patient, or any observer, describes as clinical spread. We found in the survey of these cases that when the lesion had been described as clinically spreading, enlarging, or growing by the patient or physician for more than three months that none of those patients survived. That is not the same as microscopic spread. We realize that most patients do not observe the earliest minute changes of malignancy clinically.

One other point I want to make is this: Some years ago we had a blue nevus diagnosed as such by a competent pathologist, and it developed into a malignant melanoma. We asked to review the slides, and a number of pathologists went over them and agreed that it was a blue nevus. It became malignant. Six weeks ago we had another similar case, that of a man of 30 years, who had a lesion on the ear, which a competent surgeon had removed, as he thought, widely. An extremely competent pathologist made the diagnosis of blue nevus. It recurred. Again the surgeon removed it, and another diagnosis of blue nevus was made. Two other pathologists agreed. Six months after the last removal it recurred again, and a number of lesions developed on the ear. I saw the case clinically. The tumor was a malignant melanoma with a metastatic postauricular gland.

I think the statement in the literature, that blue nevi seldom, if ever, develop malignancy is a dangerous one even if this occurs only a very few times. The tumor still must be regarded as potentially malignant, and, when malignancy does occur, it is almost always a tragedy, as in these two cases.

Dr. Francis A. Ellis, Baltimore: I enjoyed this paper very much but wish to object to using the word "nevus" when we really mean moles, because, as a dermatologist and the dictionary recognize, there are all sorts of nevi besides moles.

Along with Dr. Andrews, instead of just the clinical differentiation between the junction nevus and lentigo maligna, I should like to know Dr. Becker's histologic differentiation of these two. As far as I am concerned, the acquired lentigo maligna is the same as a late junction nevus.

Dr. S. William Becker, Chicago: I appreciate this discussion very much.

Some of the differences are matters of terminology, but I shall try to answer them. Dr. Driver called attention to wrong diagnoses. I have seen good pathologists make mistakes in this particular field. In my own instance, I have never advised an operation until I have had consultation with a good surgical pathologist who I know is excellent in this particular study.

Dr. Driver and Dr. MacVicar were very fortunate because they had a very small percentage of metastases in the patients whom they treated, for Clark and MacDonald showed that from 40 to 60% in a fairly large series had metastases when they first came to the physician.

Dr. Beerman's criticism of the term "melanoma" is also justified. The British and the Australians use "melanoma" for pigmented nevus and "malignant melanoma" for what we call melanoma. Probably, if we were scientifically accurate, we should have to call a pigmented nevus a melanoma, and what we call melanoma, a melanoma sarcoma. It is a nonepithelial tumor and therefore should be a sarcoma.

By "melanotic carcinoma" I mean what is usually called by dermatologists melanotic epithelioma.

Dr. Andrews wanted the clinical differentiation between lentigo maligna and a junction nevus. Lentigo maligna spreads more rapidly than a junction nevus, that is, an ordinary junction nevus in adult life will remain stationary, whereas lentigo maligna spreads slowly, sometimes reaching the size of several centimeters.

Dr. Hutchinson was the first man to call attention to these acquired brown spots, and his diagnosis was purely clinical, on microscopic examination some of the spots were simple lentigo, some were melanoma, and some were pigmented carcinoma.

Dr. Osborne talked about the spread. I think patients that he mentioned, in whom the physician had stated that the tumor was growing clinically, had already reached the tumor stage, and, as Campbell DeMorgan said, from then on it spreads throughout the body. But our function is to get these patients before they reach the tumor stage. I have seen these brown spots that have been present for at least 10 years, although that is not a safe time to leave them there. The patient may develop metastases after three or four or five years.

I think blue nevi do become malignant, but I went over Professor Darier's cases carefully, and there is no real case of malignancy. There were no autopsy findings; there were no signs of real malignant spread of melanoma. There have been a few others reported, but I have never seen one. I don't think Dr. Montgomery himself has ever had one.

Dr. Osborne's case of melanoma of the ear is a good argument for early radical surgical treatment. In a recent article on treatment of melanoma of the ear, it stated that it is fortunate that the lymph nodes are so close to the ear, because the surgeon simply takes the ear off, and takes all the lymph nodes off, an operation which is, of course, rather radical.

Dr. Ellis talks about nevus and mole. That is very difficult. When Dr. Obermayer and I wrote our textbook, we went over that problem, and we decided that we would limit the term "nevus" to lesions containing nevus cells, and epithelial nevi, nevus unilateralis.

I thought I explained that in the section of a so-called junction nevus from the sole of the foot, the cells were only benignly neoplastic. There was no sign of malignancy whatever. In lentigo maligna, with the large succulent cells—and, incidentally, sometimes you will get fusiform cells in these tumors—the anaplastic cells, working their way through to the surface and spreading, of course, into the dermis eventually, and the round cell infiltrate. Those you never see in a quiescent nevus.

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THE REDDISH-ORANGE FLUORESCENCE OF NECROTIC CANCEROUS SURFACES UNDER THE WOOD LIGHT

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IN THE year 1903 R. W. Wood utilized ultraviolet radiations passed through a nickel oxide filter to remove visible light. This invention has proved useful in medicine, science, arts, industry, theater, and elsewhere. In a dark room under the Wood light illumination many things invisible under ordinary conditions become visible. The Wood light makes certain minerals or printed cloth fluoresce in a peculiar variety of shades. Focused on an old painting, it makes the older colors fade almost completely and brings out distinctly the recent restorations. Lipstick marks in soap-washed faces or on laundered table napkins appear clearly as pale yellow spots. Figures or letters on laundered underwear or on forged checks, food contamination by rodent or insects, impurities in cocoa, flour, etc., invisible in ordinary light, appear clearly under the Wood light.

In a dark room, a beam of Wood light focused on the skin makes it appear as a ghastly mixture of increased purplish-brown pigmentations over each freckle, scar, or enlarged blood vessel, a palette of colors from face powders, creams, lotions, perfumes, lipsticks, etc. Any thickening or scaling of the skin appears pearl white. The teeth if natural appear as fluorescent pearl-white, as does ivory, but if artificial they are seen as violet-black or lemon-green. A few invisible white hairs appear vividly white.

In dermatology the Wood light is of distinct value in the diagnosis of one of the most stubborn and costly diseases of childhood, ringworm of the scalp.*

Tinea versicolor may be distinguished from leucomelanoderma, appearing as light golden-yellow powdered islands. In vitiligo the normal or hyperpigmented areas appear brown-black; the nonpigmented areas, white.

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., April 26, 1952.

Associate Professor of Clinical Dermatology, Boston University School of Medicine, Dermatologist-in-Chief, Rhode Island Hospital (Dr. Ronchese); Professor of Biochemistry, Boston University School of Medicine (Dr. Walker); Bacteriologist, Rhode Island Hospital (Dr. Young).

* References 1 and 2.

A case in which industrial compensation was asked for vitiligo of the dorsal aspects of the hands claimed due to chemical burns was cleared up satisfactorily for the claimant when vitiligo was shown to him on his feet, which appeared normal in ordinary light but clearly vitiliginous under the Wood light.

Hirschfeld [3] showed its usefulness in doubtful cases of scabies by painting the skin with diluted fluorescein, washing the dye out, and observing the outlines of the burrows brought out by the Wood light.

Roffo and Roffo, cited by Ronchese,[2] studied senile keratoses under the Wood light. According to these authors, the more precancerous the keratoses the more

Fig. 1.—*Technique.* The technique is simple. An area that can be held still for the necessary time exposure of at least 30 seconds is preferable. After focusing has been done as usual, the light is turned out. The source of illumination (Wood light lamp) is held by the operator with one hand. A fixed support is not suitable because the beam must be constantly moved to be directed to the most fluorescing spots. The other hand operates the time shutter. This is open for the desired time and then closed. The Ektachrome film is processed as for an ordinary color exposure.

they fluoresce white because of their higher cholesterol content. If confirmed, these observations will be important in dermatology.

All hyperkeratotic conditions, like warts, calluses, lichen verrucosus, keratosis pilaris, ichthyosis, psoriasis, false tinea amiantacea (seborrhea sicca) fluoresce vividly white, as do the nails. Molluscum contagiosum does not fluoresce except for the umbilication. Xanthoma and xanthelasma palbebrarum, consisting entirely

of cholesterol, do not fluoresce but appear as dark-brown little freckles or other hyperpigmented spots, since there is no hyperkeratosis.†

Smooth senile keratoses of the lentigo type (known to the layman as liver spots) are very dark under the Wood light.

A reddish fluorescence of the normal coating of the tongue, in comparison with the absence of fluorescence in vitamin B deficiency, has been studied recently by Hagerman and Hirschfeld.[3a] Figge and associates ‡ studied the red fluorescence in vaginal discharges, aiming to demonstrate a possible relation to cancer. The peculiar "live coal" red fluorescence of ulcerated epidermoid carcinomas, in con-

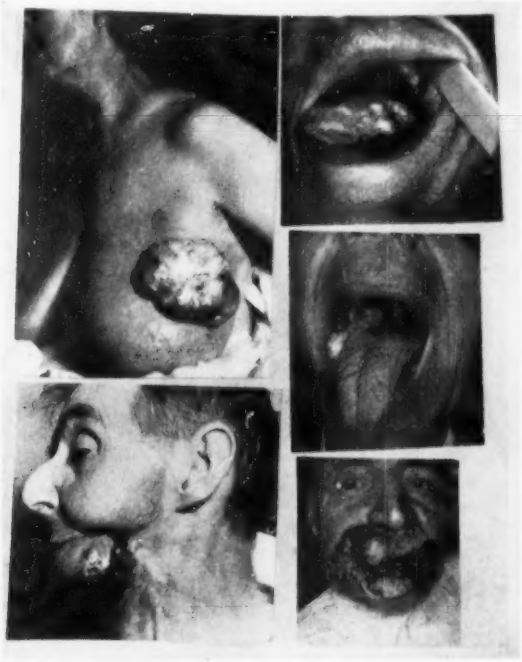


Fig. 2.—The type of neoplasm (epidermoid carcinoma with sloughing necrotic areas) which fluoresces vivid reddish-orange under the Wood light as shown in figures 4, 5, 6, 7, and 8.

trast with the nonfluorescing ulcerated basal cell ones, was extensively discussed in the paper of Gougerot and Patte [8] in 1939. They mention Policard as having

† The terms fluorescence and luminescence have been used as synonyms. They are not. Fluorescence is defined in Dorland's Medical Dictionary (Ed. 22) as "The property of emitting light after exposure to light, the wavelength of emitted light being longer than that of the light absorbed." In general, fluorescence occurs only during or immediately after excitation of a chemical substance by exposure to light of short wavelength. Luminescence is simply the property of emitting light which may be the result of a chemical reaction as in the firefly or may depend upon previously photochemically activated reactions. The concept of luminescence includes all instances where light is emitted except by objects at a high temperature. The phenomena described in this paper are in the class of fluorescence.

‡ References 4 to 7.

noticed in 1924 the brick-red fluorescence in experimental cancer of the rat in four cases. They give credit to Margarot and Deveze (1929) as the first to report the fluorescence of spontaneous cancers, saying that "in some cases they noticed an orange color in cancerous surfaces." They quote Körbler (1931) as describing red fluorescence in cancers of the neck, breast, and nose, and Thomas (1934) as describing red fluorescence in two cases of chloroma and in cervical metastases of the same tumor. Gougerot and Patte,[8] in a previous paper (1938), described the "striking vermilion red" fluorescence of an ulcerated vegetating squamous cell epithelioma, while surrounding leucoplakic areas did not fluoresce but appeared as dark red-violet and the tongue showed "the normal orange color," with some areas slightly deeper orange. Further in their paper they write of having found the

Fig. 3.—The types of neoplasm or chronic ulcerated purulent lesion which does not fluoresce but appears under the Wood light as deep violet: *1* and *2*, basal cell epithelioma; *3*, long-standing, deeply ulcerated roentgen rays dermatitis; *4*, long-standing deep purulent ulcer (ankle); *5*, deep devitalized ulcer following radiations for epidermoid carcinoma (an eventual demonstration of cure). Biopsy specimens from Nos. 3, 4, and 5 were inflammatory tissue.

striking live-coal-red fluorescence in six more cases of squamous cell epithelioma. A translation of the colorful French description is as follows: "red, deeply carmine or orange, surrounded by a dark border, intensely fluorescent, incandescent, like live coals stirred by the wind, or as if the tumor had been illuminated from within by a powerful red lamp . . . a necrotic ulcer vividly fluorescing red, making one think of the incandescent live coal under the ashes. . . ." They eliminated sources of errors (ointments, dressings, etc.). The pathology has been constantly squamous cell epithelioma. They stress the fact that the surface must be necrotic (*sanie*

cancéreuse) and that the fluorescing part is only the necrotic superficial part of the lesion. The cut surface of surgical specimens does not fluoresce except for the part corresponding to the surface. They quote Policard as attributing the fluorescence to the presence of hematoporphyrin in relation to the presence of a microbic superimposed process. They quote Körbler as attributing it to cancer tissue metabolism and not to the microbic flora. Gougerot and Desgrez ‖ tried to identify the porphyrins by the Thomas method, their conclusions favoring a special process of disintegration of hemoglobin. In the discussion following the presentation of the Gougerot and Patte paper, Jausion remarked that the flora on the surface of fermented cheese fluoresce identically under the Wood light. We are unable to confirm this statement on the cheeses available here. In a personal communication dated Dec. 10, 1946, Professor Gougerot stated that the peculiar fluorescence has been a constant finding, ever since the publication of his paper, in squamous cell epitheliomas of the skin, mucous membranes of the mouth, genitals, and cervix.

Clinical observations in over 50 cases during the last five years at the Tumor Clinic of the Rhode Island Hospital confirmed the Gougerot and Patte[8] observations. The "live coal" fluorescence, which, according to the National Bureau of Standard Color Name Designations and the Munsell Book of Colors,[9] can be defined as vivid reddish-orange, is found only in advanced ulcerated necrotic epidermoid carcinoma. It impregnates dressings and surrounding areas. Basal-cell epithelioma (no matter how badly ulcerated), carbuncle, ulcerated hemangioma, long-standing stasis ulcer (no matter how extensive and purulent), pseudoepitheliomatous hyperplasia, ulcerated leproma,[10] tubercular and syphilitic gumma, and ulcerated granuloma fungoides do not fluoresce but assume a uniform deep-violet discoloration. The fluorescence is a surface phenomenon. A section through the tumor will reveal no fluorescence below the surface. Roentgen therapy reduces the fluorescence considerably. After a few days if roentgen therapy is not continued the fluorescence reappears as vivid as before.

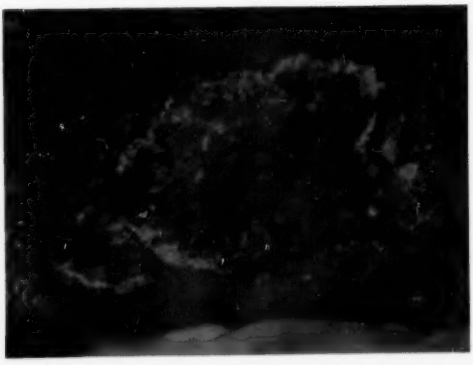
Multicolored flowers, leaves, half-green half-red fall-changing leaves, forest fungi and lichens, and Brazilian butterflies were observed under the Wood light to see if a similar shade of orange-red could be elicited. Almost all varieties of colors are dulled out in a uniform violet discoloration. Chemicals, ointments, creams, cosmetics, and ointment bases in common external use fluoresce in various shades from terra cotta to canary yellow, but we have found none leaning toward red. (The grayish ultroine ointment fluoresces very white, the colorless Vi-Dom-"A" cream fluoresces canary yellow, the petrolatum-like Aureomycin ointment also fluoresces vividly yellow, as do the clothes contacting the treated areas).§ Mysteri-

‖ Gougerot and Desgrez, cited by Gougerot and Patte.

§ In a recent paper by Michaelides, P., and Shatin H. R., Erythrasma Fluorescence under the Wood Light, A. M. A. Arch. Dermat. & Syph. **65**:614 (May) 1952, a red fluorescence is reported as a frequent finding and as valuable in the clinical diagnosis of erythrasma. I examine under the Wood light most of my private and clinic patients and this naturally includes many cases of erythrasma. I recall two instances of a genitocrural figurated or gyrated vivid deep-purple-red fluorescence, beautiful to look at, which I thought very peculiar and interesting. Because of the darkness of its red, probably, it will be difficult to photograph.

I did not connect the fluorescence with erythrasma because almost all my cases appearing clinically as erythrasma showed a deep violet outline, and no fluorescence of any kind or shade. If further investigation confirm the observation of Michealides and Shatin another laurel will be added to the practical value of the Wood light in everyday practice.

Figure 4 (below and left).



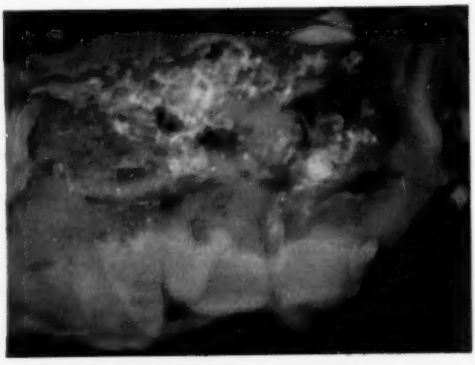


Figure 5 (above and right)

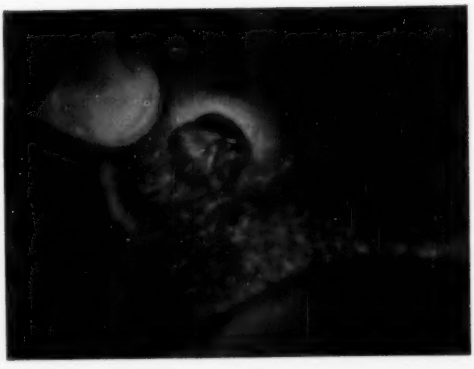


Figure 6 (above and left).

Fig. 4.—Left, ordinary color photograph (Ektachrome, type B, no filter, opening *f*/11, time ½ second, illumination flood light 3,200° K-500 W.). Right, the same view, the same kind of film and a 2A Wratten filter, opening *f*/4.5, time 60 seconds, illumination a Wood light lamp (110-120 volts, 60 cycles, A.C., a mercury vapor bulb, the Corning nickel filter, 4.5 mm. thick, transmitting the band around 3,660 A.).

Long-standing stasis leg ulcer. The areas fluorescing reddish-orange are epidermoid (squamous cell) carcinoma. The nonfluorescing areas are inflammatory, or pseudoepitheliomatous hyperplasia.

Fig. 5.—The surgical dressing carrying the discharge from a carcinoma of the breast was used in preference to a photograph of the breast itself, because of the length of exposure. A breast view usually is blurred after an exposure of 30 seconds. The photograph at the left was taken as routinely for color photography (Ektachrome, type B film, no filter, opening *f*/11, time ½ second, illumination flood light 3,200° K, 500 W.). The photograph at the right was the same view taken with the same kind of film and a 2A Wratten filter, opening *f*/4.5, time 60 seconds, illumination a Wood light lamp (110-120 volts, 60 cycles, A.C., General Electric H-100 FL 4 mercury vapor bulb, with in front the Corning nickel filter, 5 inches in diameter, 4.5 millimeters thick, transmitting the bands around 3,660 A.).

Blood and other colored matters visible in ordinary daylight or artificial light are invisible, and appear as deep violet to the eye, blue in the film. If the dressing comes from the surface of an ulcerated squamous cell carcinoma, as in this case, other areas become visible, vividly reddish-orange in color, the characteristic shade of red found only on necrotic surfaces of ulcerated squamous cell epithelioma, more intensely and in larger quantities as the lesions are more advanced and more necrotic.

Surfaces of ulcerated basal cell epithelioma, devitalized radiation ulcers, chronic long-standing leg ulcers or other necrotic purulent lesions classified as noncancerous will not fluoresce, but appear of a uniform deep violet color to the eye, uniform blue in the film. As far as we know, there is no chemical, ointment, culture, or other living or dead material producing a similar shade of red, except calcite.

Fig. 6.—This lesion was subjected to biopsy three times and found inflammatory. Treatment was postponed. A fourth biopsy was directed at the pink spot under the beam of Wood light and epidermoid carcinoma grade II was found.

Figure 7 (below and right).

Figure 7 Ulcerated squamous cell epithelioma of hand.

Figure 8 Ulcerated carcinoma of cheek metastatic from lip.

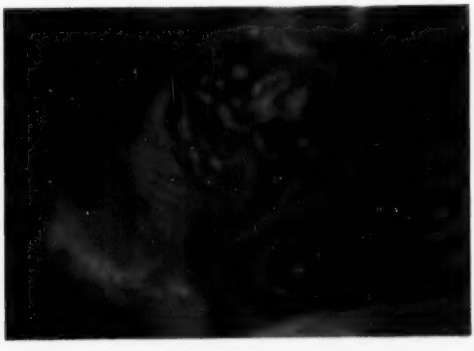


Figure 8 (above and right).

ous diagnostic powers are believed to be possessed by the examining physician if on a normal-appearing face he shows the patient vividly yellow eyelids and *en berloque* streaks across his or her face, if he or she has used the popular remedy against "tired eyes," Murine, because of its content of tincture of merthiolate.

Also, a patient may be quite surprised at the examiner's diagnostic ability if he tells him, by looking at his nails, that he is taking or has taken quinacrine hydrochloride (Atabrine).

While the observations of these very interesting phenomena are easy office procedures, their recording on a color film for demonstration in print or on the screen presents considerable difficulty. So far, what the eye sees in a dark room under a beam of Wood light in ringworm of the scalp or quinacrine hydrochloride nails has been demonstrated by hand coloring of black-and-white photographs. The most vivid light-green fluorescence of Microsporum-audouini-infested hairs produces on the color film a shade of white with so little green that there is no value in it for screen or printing demonstration. The same poor result is obtained with quinacrine hydrochloride nails. The film is uniformly blue.

Naturally, it was very gratifying to see the fluorescence of epidermoid carcinoma register satisfactorily in the color film, because of the vividness of the shade of red. As has been mentioned before, the peculiar fluorescence of epidermoid carcinoma, in contrast with basal cell carcinoma, was observed and discussed in France about 20 years ago. As far as we know, no further investigation of this particular phase of fluorescence has since appeared in the literature. We assume that the reason is, first, that the biological factors remained unknown, and, second, the lack of demonstrative color illustrations.

Material for bacterial investigation was obtained from four cases of advanced carcinoma showing reddish-orange fluorescing areas under the Wood light.

REPORT OF CASES

Case 1.—This was a 70-year-old man with an advanced ulcerated carcinoma of the palate. Scrapings were cultured in four different kinds of bacteriologic media: blood veal infusion agar, plain nutrient agar, thioglycolate broth, dextrose nutrient broth. After appropriate incubation at 37 C. various types of colonies were picked off in pure culture from the agar streak plates. The organisms identified in pure culture included the following: hemolytic Staphylococcus aureus (predominating species), Staphylococcus albus, streptococci of the viridans group, diphtheroids, and hemolytic streptococci (few colonies).

When exposed to the Wood light, none of the mixed or pure cultures listed above showed any fluorescence.

Case 2.—A 65-year-old woman had an ulcerated adenocarcinoma of one breast. Scrapings were cultured in the following media: blood nutrient agar, plain nutrient agar, thioglycolate broth, dextrose nutrient broth, and Sabouraud's medium. After an appropriate incubation period at 37 C., various types of colonies were picked off in pure culture from the agar streak plates and identified as follows: anaerogenic paracolon bacilli Type 29911, Staph. albus, spore former (aerobic type), and a viridans Streptococcus.

When these pure and mixed cultures in the various media were exposed to the Wood light they failed to show any fluorescence.

Case 3.—The patient was a 70-year-old woman with an ulcerated carcinoma involving the entire perineal region. Scrapings were cultured in blood veal infusion agar, plain nutrient agar, Sabouraud's agar, thioglycolate broth, and dextrose nutrient broth. After incubation for an

appropriate period at 37 C., various types of colonies were picked off in pure culture and identified as follows: hemolytic Staph. aureus, Proteus mirabilis (predominating species), Escherichia coli, Aerobacter aerogenes, paracolon bacilli types, and enterococci.

When these pure and mixed cultures in the various media were exposed to the Wood light they failed to show any fluorescence.

CASE 4.—This was a 65-year-old man with a long-standing carcinoma of one foot. Scrapings from fluorescing areas were cultured in the following media: trypticase soy blood agar, plain nutrient agar, Sabouraud's agar, eosin methylene blue agar, Salmonella and Shigella agar, thioglycolate broth and trypticase soy-dextrose broth. After an appropiate incubation period at 37 C. various types of colonies were picked off in pure culture from the agar streak plates and identified as follows: proteus vulgaris (predominating species); aerobacter aerogenes, gram-positive micrococci (tetracocci); enterococci; anaerobic streptococci and bacterioides species.

When these pure and mixed cultures in the various media were exposed to the Wood light, they failed to show any fluorescence.

From the limited number of cases studied in which no red fluorescence or an uncertain fluorescence was elicited in cultures and in which no difference was noted in the organisms obtained in fluorescing and non-fluorescing areas, no conclusion can be drawn as to the relation between the cultivated organisms and the red fluorescence, unless factors present in the necrotic cancer tissue are not simulated sufficiently in the artificial medium.

It has been possible, on further investigation of Case 1, to isolate and identify a micro-organism which can be shown to produce a similar fluorescence under laboratory conditions. This organism is not properly a bacterium, but has the characteristics of the genus Streptomyces. The fluorescence which is of the bright red color characteristic of the lesions previously described occurs only when this organism is grown on a culture medium which contains blood. The organism was first isolated from scrapings from the patient's palatal tumor. The scrapings themselves fluoresced scarlet under Wood's filtered ultraviolet light. The cultures have been grown and carried on Sabouraud's medium and were observed by us to have the following cultural characteristics:

Glucose agar. Fast and abundant growth which is folded, spreading, raised, and cream-colored. White powdery aerial mycelium appear on top.

Glucose broth. White, fluffy growth that settles to bottom.

Gelatin. Liquefaction very slow but takes in the whole tube. Amber-colored growth around the top of tube in a ring. It resembles the folded growth on glucose.

Litmus milk. Very thin cream with no change in milk.

Starch broth—hydrolzed. Abundant growth on top of tube; the rim is brown, like a pellicle with white mycelium; at the bottom is white fluffy growth.

Potato slant. No growth.

Czapek's agar. About fourth day thin growth of small white colonies is seen, later they become yellow-green with tiny white aerial mycelium.

Broth. Nitrites were produced from nitrate in medium (sulfanilic acid and alpha naphthalmine used).

Glucose-asparagin. Large amount of white to cream-colored growth which is raised and glistening, some aerial mycelium.

Fluorescence. Appeared only on media that contained blood.

These characteristics did not permit us to make an identification of this organism with any known species of Streptomyces.

Dr. Selman A. Waksman, chairman of the department of microbiology at Rutgers University, New Brunswick, N. J., studied the organism and succeeded

in identifying it as belonging to the Streptomyces albus group. For the present it is named by Dr. Waksman Streptomyces albus No. 3564. Dr. Waksman gives its cultural properties as follows:

It grows well on some media and not readily on others. It produces white cottony aerial mycelium, with straight sporulating hyphae.

1. Czapek's agar. Thin, spreading growth, undersurface brownish with darker brown spots, medium slightly darkened; aerial mycelium cottony white.

2. Dextrose asparagin agar. Nonpigmented vegetative growth, a few small patches of white aerial mycelium. No pigment.

3. Nutrient agar. Thin creamy-colored growth with aerial mycelium, white, cottony. No soluble pigment.

4. Yeast-dextrose agar. Good, spreading growth; undersurface dark brown; medium completely darkened; aerial mycelium fluffy white.

5. Gelatin tube. Lichenoid heavy, cream-colored growth, rapid liquefaction of gelatin; abundant white aerial mycelium; no soluble pigment.

6. Potato plug. No growth.

SUMMARY AND CONCLUSIONS

The peculiar vivid reddish-orange fluorescence elicited by the Wood light from necrotic ulcerated surfaces of squamous cell epithelioma in contrast with the uniform deep violet discoloration of other ulcerated surfaces (basal cell epithelioma, carbuncle, tubercular and syphilitic gumma, granuloma fungoides, pseudoepitheliomatous hyperplasia, and long-standing inflammatory process) is a clinical observation valuable in ruling out the above-mentioned conditions, and offering the clinical diagnosis of epidermoid (squamous cell) carcinoma to be considered.

The red fluorescence has been regularly observed in open, necrotic adenocarcinomata of the breast and in one case of facial fibrosarcoma. It is not known what part adenomatous, sarcomatous, or epidermal cells play in the production of the red fluorescence. The only fact known is that for a lesion to elicit the fluorescence it must be a cancer, ulcerated, necrotic, and highly malignant.

From an epidermoid carcinoma of the palate an organism has been cultivated producing similar fluorescence in blood-containing media. It has been identified as belonging to the genus Streptomyces albus. Further study, we hope, will clarify the relation of this organism to the peculiar fluorescence. While the phenomenon has been discussed in the past, this is the first time satisfactory color photographs were obtained.

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COMPARATIVE EFFECTS OF NEOMYCIN AND OTHER ANTIBIOTICS ON PYOGENIC BACTERIA

In Vitro Effect on Bacteria Isolated from Cutaneous Pyogenic Infections

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THE STUDY herewith reported concerns the in vitro effect of neomycin sulfate (hereafter referred to as neomycin) and other antibiotics * on numerous strains of bacteria which were isolated from patients with various types of cutaneous pyogenic infections, including impetigo, ecthyma, pustular folliculitis, furunculosis, ulcers, paronychia, otitis externa, and secondarily infected skin conditions such as contact dermatitis, superficial fungus infections, atopic dermatitis and burns. In addition, other factors which influence the choice of an antibiotic for topical use will be discussed.

Neomycin is a comparatively new antibiotic, which was discovered in 1949 by Waksman and Lechevalier [1]; it is produced by a strain of Streptomycetes. Laboratory and clinical investigative studies of this antibiotic by the original investigators [1] and by other workers have indicated the spectrum † of the drug, which includes an unusually wide variety of both Gram-positive and Gram-negative organisms.

Early reports on the parenteral administration of neomycin by Waisbren and Spink [5] and by Carr and Brown [6] indicated that the antibiotic has ototoxic and nephrotoxic effects when it is administered in adequate dosage over a prolonged period. We are in complete agreement with the statement of Waisbren and Spink [5] that "in view of the ototoxic and nephrotoxic effects of Neomycin, this drug cannot be recommended for general use." However, a few patients with serious infections, due to organisms which are not sensitive to other antibiotics now available, may have a satisfactory therapeutic result with the parenteral administration of neomycin.

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* Neomycin sulfate and bacitracin were supplied by the Upjohn Company, Kalamazoo, Mich.; oxytetracycline (Terramycin), by Charles Pfizer & Company, Inc., Brooklyn; chlortetracycline (Aureomycin), by Lederle Laboratories Division, American Cyanimid Co., Pearl River, N. Y., and Chloramphenicol (Chloromycetin), by Parke, Davis & Company, Detroit.

† References 2 to 9

and, under these circumstances, the risk of toxic effects and even permanent deafness may be justified; this would not apply in the case of cutaneous pyogenic infections which do not endanger life.

Poth and associates[10] have reported on an extensive experience with the oral administration of neomycin for intestinal antisepsis. They concluded that the combination of neomycin in a dosage of 1 gm. orally every four hours with phthalylsulfathiazine (sulfathalidine) (1.5 gm. every 24 hours) is effective preoperative treatment for surgery of the gastrointestinal tract. They reported that only a small amount of neomycin was absorbed from the bowel, and therefore they concluded that even in a person highly sensitive to neomycin serious toxic damage would not be expected to occur.

Reports regarding the topical use of neomycin in the treatment of cutaneous pyogenic infections which have been published ‡ to date have been very favorable, and it would appear that the drug has become established as one of the topical therapeutic agents of choice for the treatment of bacterial infections of the skin. It remains to be determined whether additional experience will modify or confirm our present opinion regarding the comparative effectiveness of neomycin and its apparent low irritant and sensitizing potential when it is used topically.

The relative effectiveness and the indications for the topical use of bacitracin, chlortetracycline (Aureomycin), and oxytetracycline (Terramycin), as well as other antibiotics and drugs have been summarized by Sulzberger and Baer[16] in their excellent review article on the treatment of cutaneous pyogenic infections which appeared in the "1950 Yearbook of Dermatology and Syphilology." Indeed, there are numerous reports in the literature on the topical use of bacitracin and chlortetracycline in the treatment of cutaneous pyogenic infections. One of these papers is that of Miller, Slatkin, and Johnson,[17] who have had extensive experience with bacitracin; another is that of Sawicky, Pascher, Frank, and Rosenberg,[18] who treated a large series of patients with chlortetracycline ointment. These clinical reports and those of numerous other investigators will not be reviewed in detail, but it is appropriate to note that it seems to be the prevailing opinion of many dermatologists, including Pillsbury § and Osborne,‖ that, in general, bacitracin is a less effective topical therapeutic agent for bacterial infections of the skin than chlortetracycline, oxytetracycline, and neomycin and that tyrothricin and gramicidin are inferior to bacitracin. Reports of clinical experience in regard to the topical use of chloramphenicol, polymyxin B, and combinations of antibiotics (tyrothricin and bacitracin,¶ polymyxin B and bacitracin,# and neomycin and gramicidin *) are limited and critical analysis of the present status of these topical preparations is not possible at this time. It is doubtful that these antibiotics and combinations of antibiotics will prove to be more effective than neomycin, chlortetracycline, and oxytetracycline except that polymyxin B (especially in combination with other antibiotics) should

‡ References 11 to 15.

§ Pillsbury, D. W.: Special Lecture on Bacteriology of the Skin, read before the 71st Annual Session of the American Academy of Dermatology and Syphilology, Chicago, Dec. 8, 1951.

‖ Osborne, E. D.: Personal communication to the authors, Jan. 1952.

¶ The preparation used was Tyrotrace ointment (Sharp & Dohme, Inc.).

The preparations used were Polysporin (Burroughs Wellcome & Company, Inc.) and Polycin Ointment (Pitman-Moore Company, Division of Allied Laboratories, Inc.).

* The preparation used was Spectrocin Ointment (E. R. Squibb & Sons).

be a useful addition to our therapeutic armamentarium for the treatment of Pseudomonas infections, although it is effective against other types of Gram-negative bacterial infections. We have had some experience with polymyxin B, but it was not included in this study. The vast majority of dermatologists agree that the high incidence of sensitization reactions following the topical use of penicillin precludes the use of the antibiotic in this manner.

MATERIALS AND METHODS

The tube dilution test was used exclusively. Twofold serial dilutions of the antibiotic were made in a broth medium suitable for the respective organism. Bacto-tryptose-phosphate broth

TABLE 1.—*In Vitro Sensitivity of 377 Strains of Bacteria to Neomycin*

Organism *	No. of Strains Inhibited by Varying Concentrations (γ/Cc.) of Neomycin							Total No. of Strains Tested
	0.4 or Less	0.6-2	4-6	8-10	15-25	50	More Than 50	
H † Staph. aureus	68	10	1	0	0	0	0	79
Beta H Str.	4	15	28	19	24	13	1	104
H Staph. albus	17	0	0	0	0	0	0	17
NH Staph. albus	12	0	0	0	0	0	0	12
Proteus	0	8	35	3	1	1	0	48
Pseudomonas	0	21	28	3	0	2	0	54
E. coli	1	17	5	1	1	0	0	25
Paracolobactrum	1	15	1	0	0	0	0	17
A. aerogenes	0	12	1	0	0	0	0	13
A. fecalis	0	1	3	0	1	2	1	8

* All strains coagulase-positive.
† H indicates hemolytic; NH, nonhemolytic.

TABLE 2.—*In Vitro Sensitivity of 203 Strains of Bacteria to Oxytetracycline*

Organism *	No. of Strains Inhibited by Varying Concentrations (γ/Cc.) of Oxytetracycline							Total No. of Strains Tested
	0.4 or Less	0.6-2	4-6	8-10	15-25	50	More Than 50	
H † Staph. aureus	35	8	4	5	1	1	3	57
Beta H Str.	45	17	7	1	0	1	1	72
H Staph. albus	0	1	1	0	0	0	0	2
NH Staph. albus	0	1	1	0	0	0	0	2
Proteus	0	0	0	0	1	18	13	32
Pseudomonas	1	12	16	1	2	0	0	32
E. coli	1	16	1	0	0	0	0	18
Paracolobactrum	0	7	3	0	0	0	1	11
A. aerogenes	0	5	2	0	0	0	0	7
A. fecalis	0	2	0	0	0	0	0	2

* All strains coagulase-positive.
† H indicates hemolytic; NH, nonhemolytic.

was used for staphylococci and all Gram-negative rods which were tested. Horse meat infusion broth was used for streptococci. Five hundredths milliliter of a 1:1,000,000 dilution of a 24-hour culture of the organism was added to test tubes containing 2 ml. of the twofold dilutions of the antibiotic to be tested. It was determined that the inoculum was approximately 100 organisms per tube (1×10^2). The tubes were incubated at 37 C. for 24 hours, and the tests were read at the end of that time. Complete inhibition was recorded as the first tube which showed no growth. A control organism with a previously determined sensitivity was run with each set of tests.

RESULTS

The first group of in vitro experiments are summarized in Tables 1 to 11. It is evident that none of these antibiotics has a superior in vitro effect for all of the bacterial organisms which are isolated from patients with cutaneous pyogenic infections.

TABLE 3.—*In Vitro Sensitivity of 159 Strains of Bacteria to Chloramphenicol*

Organism *	No. of Strains Inhibited by Varying Concentrations (γ/Cc.) of Chloramphenicol							Total No. of Strains Tested
	0.4 or Less	0.6-2	4-6	8-10	15-25	50	More Than 50	
H † Staph. aureus	0	8	44	0	5	3	0	60
Beta H Strep	0	14	11	0	1	1	0	27
H Staph. albus	0	1	1	0	0	0	0	2
NH Staph. albus	0	1	0	0	0	1	0	2
Proteus	0	0	6	6	1	0	0	13
Pseudomonas	0	0	0	5	21	5	0	31
E. coli	0	3	7	0	0	0	0	10
Paracolobactrum	0	0	2	2	0	0	0	4
A. aerogenes	0	2	4	2	0	0	0	8
A. fecalis	0	1	0	1	0	0	0	2

* All strains coagulase-positive.
† H indicates hemolytic; NH, nonhemolytic.

TABLE 4.—*In Vitro Sensitivity of 131 Strains of Bacteria to Chlortetracycline.*

Organism *	No. of Strains Inhibited by Varying Concentrations (γ/Cc.) of Chlortetracycline							Total No. of Strains Tested
	0.4 or Less	0.6-2	4-6	8-10	15-25	50	More Than 50	
H † Staph. aureus	34	16	3	5	2	2	0	62
Beta H Str.	12	13	1	0	1	0	1	28
H. Staph. albus	0	2	0	0	0	0	0	2
NH Staph. albus	0	1	1	0	0	0	0	2
Proteus	0	0	0	0	0	1	6	7
Pseudomonas	0	0	0	0	6	1	1	8
E. coli	0	0	6	1	0	0	0	7
Paracolobactrum	0	1	4	2	0	0	0	7
A. aerogenes 0	0	1	5	0	1	0	0	7
A. fecalis	0	1	0	0	0	0	0	1

* All strains coagulase-positive.
† H indicates hemolytic; NH, nonhemolytic.

TABLE 5.—*In Vitro Sensitivity of 214 Strains of Bacteria to Bacitracin*

Organism *	No. of Strains Inhibited by Varying Concentrations (γ/Cc.) of Bacitracin							Total No. of Strains Tested
	0.4 or Less	0.6-2	4-6	8-10	15-25	50	More Than 50	
H † Staph. aureus	0	2	5	16	20	2	0	45
Beta H Str.	30	7	4	1	15	14	3	74
Proteus	0	0	0	0	0	0	27	27
Pseudomonas	0	0	0	0	0	0	31	31
A. aerogenes	0	0	0	0	0	0	6	6
E. coli	0	0	0	0	0	0	18	18
Paracolobactrum	0	0	0	0	0	0	11	11
A. fecalis	0	0	0	0	0	0	2	2

* All strains coagulase-positive.
† H indicates hemolytic; NH, nonhemolytic.

TABLE 6.—*In Vitro Sensitivity Tests; Coagulase-Positive Hemolytic Staph. Aureus, Fifty-Two Strains*

Antibiotic *	0.4 or Less	0.6-2	4-6	8-10	15-25	50	Greater Than 50
Neomycin	48	3	1	0	0	0	0
Chlortetracycline	31	11	3	5	2	0	0
Oxytetracycline	35	4	3	4	2	1	3
Chloramphenicol	0	8	36	0	5	3	0

* Expressed as micrograms per cubic centimeter.

TABLE 7.—*In Vitro Sensitivity Tests Coagulase-Positive Hemolytic Staphylococcus Aureus, Forty Strains*

Antibiotic *	0.4 or Less	0.6-2	4-6	8-10	15-25	50	Greater Than 50
Neomycin	36	3	1	0	0	0	0
Chlortetracycline	30	3	1	4	2	0	0
Oxytetracycline	33	0	0	3	0	1	3
Chloramphenicol	0	8	26	0	5	1	0
Penicillin	40	0	0	0	0	0	0
Bacitracin	0	2	5	16	16	1	0

* Expressed as micrograms per cubic centimeter.

TABLE 8.—*In Vitro Sensitivity Tests: Hemolytic Streptococci—Twenty-Three Strains*

Antibiotic *	0.4 or Less	0.6-2	4-6	8-10	15-25	50	Greater Than 50
Neomycin	2	4	7	8	2	0	0
Chlortetracycline	11	9	1	0	1	0	1
Oxytetracycline	17	3	1	0	0	1	1
Chloramphenicol	0	14	7	0	1	1	0
Penicillin	19	4	0	0	0	0	0
Bacitracin	10	2	3	0	3	5	0

* Expressed as micrograms per cubic centimeter.

TABLE 9.—*In Vitro Sensitivity Tests: Hemolytic Streptococci—Sixty-Two Strains*

Antibiotic *	0.4 or Less	0.6-2	4-6	8-10	15-25	50	Greater Than 50
Neomycin	4	15	17	12	12	2	0
Oxytetracycline	42	12	6	0	0	1	1
Bacitracin	24	6	5	2	16	8	1

* Expressed as micrograms per cubic centimeter.

TABLE 10.—*In Vitro Sensitivity Tests: Pseudomonas, Six Strains*

Antibiotic *	0.4 or Less	0.6-2	4-6	8-10	15-25	50	Greater Than 50
Neomycin	0	1	3	2	0	0	0
Chlortetracycline	0	0	0	0	4	1	1
Oxytetracycline	0	1	3	0	2	0	0
Chloramphenicol	0	0	0	0	4	2	0
Penicillin	0	0	0	0	0	0	6
Bacitracin	0	0	0	0	0	0	6

* Expressed as micrograms per cubic centimeter.

TABLE 11.—*In Vitro Sensitivity Tests: Proteus, Five Strains*

Antibiotic *	0.4 or Less	0.6-2	4-6	8-10	15-25	50	Greater Than 50
Neomycin	0	0	3	1	1	0	0
Chlortetracycline	0	0	0	0	0	0	5
Oxytetracycline	0	0	0	0	0	0	5
Chloramphenicol	0	0	4	0	1	0	0
Penicillin	0	0	3	2	0	0	0
Bacitracin	0	0	0	0	0	0	5

* Expressed as micrograms per cubic centimeter.

If only these in vitro tests are considered in the appraisal of the antibiotics which were studied (exempting penicillin for reasons which will be explained later), the relative order of effectiveness of the antibiotics for the important bacterial organisms which cause cutaneous pyogenic infections is as follows:

TABLE 12.—*Antibacterial Spectrum* of Antibiotics Which Are Recommended for Local Treatment*

Antibiotics	Hemolytic Staphylococci (Coagulase Pos.)	Hemolytic Streptococci	Proteus	Pseudomonas	Miscellaneous Gram-Negative Bacilli
Aureomycin	+++	+++	—	+	+++
Bacitracin	++	++	—	—	—
Chloramphenicol †	+++	+++	+++	++	++
Gramicidin ‡	..	..	..	..	..
Neomycin	++++	++	+++	+++	+++
Polymyxin B	—	—	+	++++	±
Oxytetracycline	+++	+++	±	+++	+++
Tyrothricin ‡	..	..	..	..	..

* Based on in vitro sensitivity tests and clinical experience. In this table, ++++ indicates superior to other available antibiotics; +++, excellent but not superior to other available antibiotics; ++, satisfactory to excellent effect in high percentage of cases; +, definitely inferior to other available antibiotics; ±, questionable effect, and — no effect.

† We have had very little experience with the local use of chloramphenicol, and the evaluation in this case applies only to in vitro tests.

‡ We have not evaluated these antibiotics because they were not included in our in vitro study; the clinical use of these drugs has decreased because of the availability of other antibiotics.

TABLE 13.—*In Vitro Sensitivity Tests: Comparative Sensitivity of Fifteen Strains of Hemolytic Streptococci to Six Antibiotics*

Identification No. of Culture	Sensitivity in Micrograms/Cc.					
	Neomycin	Chlortetracycline	Oxytetracycline	Chloramphenicol	Penicillin	Bacitracin
234	0.4	0.6	0.4	4	0.02	50
235	10	0.8	0.6	4	2	50
236	0.6	0.6	0.4	2	0.02	0.6
237	8	0.4	0.2	2	<0.02	0.08
238	6	<0.2	<0.4	<1	0.2	<0.6
239	10	0.4	0.4	2	<0.02	6
240	4	0.4	0.2	4	<0.02	50
241	4	0.4	0.2	2	<0.02	0.4
242	0.4	4	6	50	0.4	15
243	10	0.8	0.4	2	0.06	50
244	15	0.8	0.6	4	2	25
245	8	50>	100	4	1	50
246	0.6	0.6	0.2	2	<0.02	0.4
247	2	0.4	0.2	2	<0.01	0.4
248	6	0.4	0.4	2	<0.01	0.6

(*a*) Hemolytic Staphylococcus aureus—Neomycin, oxytetracycline, chlortetracycline, chloramphenicol, and bacitracin.

(*b*) Hemolytic Streptococcus—Oxytetracycline, chlortetracycline, bacitracin, chloramphenicol, and neomycin.

(*c*) Pseudomonas—Neomycin, oxytetracycline, and chloramphenicol; practically no effect with chlortetracycline; no effect with bacitracin.

(*d*) Proteus—Neomycin, chloramphenicol; practically no effect with oxytetracycline and chlortetracycline.

The estimated antibacterial spectrum for each of these antibiotics as well as polymyxin B, tyrothricin, and gramicidin is presented in Table 12. In compiling this table, we have attempted to consider the laboratory data and clinical reports of numerous investigators as well as the results of our in vitro tests and clinical experience.

TABLE 14.—*The Effect of the Size of the Inoculum on In Vitro Sensitivity Tests to Neomycin*

Organism	Identification No. of Culture	1×10^2	1×10^4	1×10^5	1×10^6
Streptococci hemolytic	30677-1b	2	6	>10	10
	30766-1	4	6	>10	>10
	30585-1	2	6	8	8
	30549-1	2	6	2	>10
	30630-1	<1	6	8	4
Ps. pyocyanea	30723-2	4	6	>10	>10
	30739-3	4	6	>10	>10
	30743-1	4	6	8	8
	30864-3	2	6	8	>10
	30872-1	4	4	6	10

* The sensitivity is expressed in micrograms per milliliter.

TABLE 15.—*Strains of Bacterial Organisms Isolated From 710 Patients with Various Types of Cutaneous Pyogenic Infections*

Organism			Total *	Percentage
Staph. aureus (Hemolytic, coagulase-positive)			473	67
Hemolytic streptococci			253	36
Staph. aureus; Hemolytic streptococci			182	26
Coliform group			86	12
A. aerogenes		34		
E. coli		27		
Paracolobactrum		21		
Aerogenoides	15			
Coliforme	5			
Unidentified	1			
Unidentified		3		
Proteus			69	10
Mirabilis		39		
Vulgaris		11		
Morganii		9		
Rettgeri		3		
Unidentified		7		
Pseudomonas			46	7
Pyocyanea		36		
Fluorescens		9		
Unidentified		1		
Alcaligenes			22	3

* This represents the total number of patients with cutaneous pyogenic infection in whom the organism was isolated, either in pure culture or in combination with one or more other strains.

In Table 13, we have tabulated the results of in vitro sensitivity tests for 15 strains of hemolytic streptococci selected at random from the large number of strains of hemolytic streptococci which were isolated from this series of patients. It is interesting to note that no one antibiotic had a superior effect in all cases, although oxytetracycline and chlortetracycline were superior in all but two cases.

As noted previously, the size of the inoculum which we used routinely was of the order of magnitude of 1×10^2, or 100 organisms. We have done a series of

tests in which inoculums of four different sizes were used for the same strains of bacteria and the same antibiotic (neomycin). It is obvious that the size of the inoculum influences the results significantly although there is considerable difference in the strains of both hemolytic streptococci and Pseudomonas which were tested. The size of the inoculum had very little effect in the case of two strains of hemolytic streptococci and two strains of Pseudomonas.

In Table 15 we have tabulated the various strains of bacterial organisms which were isolated in 710 consecutive patients who had some type of cutaneous pyogenic infection. As would be expected, hemolytic Staph. aureus and hemolytic streptococci were the predominant organisms, although one (or more) of the Gram-negative rods was isolated in 32% of patients. The combination of hemolytic Staph. aureus and hemolytic streptococci was found in 26% of cases. Indeed, various combinations of organisms were noted in the vast majority of cases, but no attempt has been made to tabulate the numerous combinations.

TABLE 16.—*Properties and Therapeutic Concentrations of Antibiotics Which Are Used for Local Treatment*

Antibiotic	Stability in Solution	Color of Ointment or Solution	Concentration of Commercially Available Ointment		Solubility in Water	Concentration of Aqueous Solution
			Skin	Ophthalmic		
Chlortetracycline *	Not stable	Yellow	30 mg./gm.	10 mg./gm.	1%	0.5-1 mg./cc.
Bacitracin †	Not stable	Colorless	500 U./gm.	500 U./gm.	4%	50-200 U./cc.
Gramicidin ‡	Stable	Colorless	0.25 mg./gm.	.....	Slight	.....
Neomycin §	Very stable	Colorless	5 mg./gm.	5 mg./gm.	50 to 100%	1-2 mg./cc.
Polymyxin B ‖	Moderately stable	Colorless	0.1-0.25%	0.1-0.25%	10%	0.1-0.25%
Oxytetracycline ¶	Not stable	Light tan	30 mg./gm.	1 mg./gm.	10% (buffered)	0.5-1 mg./cc.
Tyrothricin	Stable	Colorless	0.5 mg./gm.	.....	Slight	0.5-0.33 mg./cc.

* Available as Aureomycin Ointment (Lederle) and in 50 mg. soluble tablets.
† Available as Baciguent Ointment (Upjohn), Bacitracin Ointment (Abbott, Commercial Solvents Corporation, and Lilly). Also in powder form for preparing solutions.
‡ Available as Gramoderm Ointment (Schering).
§ Available as Myciguent Ointment (Upjohn) and 50 mg. tablets of neomycin sulfate available in the near future.
‖ Available as Aerosporin Ointment (Burroughs-Wellcome).
¶ Available as Terramycin Ointment (Pfizer) and the capsules may be used for solutions.

COMMENT

Our results seem to be in general agreement with those of other investigators.† However, it is emphasized that it is difficult and indeed impossible to make a direct comparison of results in all cases. It is well known that numerous factors may influence in vitro sensitivity tests, including the medium used, the size of the inoculum, the age of the culture, and the period of incubation. These factors have been discussed in a recent paper by Waibren and his associates.[19] Their data indicate that an inoculum of approximately 1,000,000 (1×10^6) organisms of an 18-hour growth is the most suitable number of bacteria for use in the multiple tube test. Furthermore, they found that the size of the inoculum is of particular importance in detecting penicillin-resistant strains of Staph. aureus; we are in agreement with this finding, and it is for this reason that we consider our in vitro results with penicillin of little significance. The size of the inoculum is of less importance in the case of other antibiotics. It seems quite obvious that the number of micrograms per milliliter required to inhibit growth would have been increased significantly for all antibiotics and all organisms which were included in the study if we had elected to

† References 1, 2, 3, 4, 5, and 19.

use a larger inoculum. However, with the exception of penicillin, it is probable that the comparative results as regards the antibiotics which were studied would have been similar if an inoculum of 1×10^6 had been used instead of the inoculum of $1 \times 10.^2$ At the present time, we are using a larger inoculum, and subsequently we will report these results and compare them with those which have been presented in this paper.

Clancy [20] has reported that Proteus and Pseudomonas strains tend to develop resistance to neomycin, as evidenced by their ability to be brought stepwise to withstand many times the concentration of neomycin that they were able to endure on primary isolation. We have not attempted to train strains of Pseudomonas, Proteus, or other organisms to grow in high concentrations of neomycin by repeated transfer to media containing sublethal concentrations of the antibiotic. However, we have the impression, which is not yet confirmed, that from a clinical standpoint there seems to be less tendency for bacterial organisms, including Pseudomonas and Proteus, to develop resistance to neomycin after prolonged topical application of the antibiotic than there is in the case of other antibiotics.

It is difficult to correlate in vitro sensitivity results with clinical experience as regards topical use of an antibiotic in the treatment of a cutaneous infection. One reason for this is that factors other than the bacterial organisms which are isolated influence the course of bacterial infections of the skin; also serum, purulent exudate, and enzyme systems of the skin may interfere with the action of the antibiotic. We have had considerable experience with the use of neomycin, chlortetracycline, bacitracin, and oxytetracycline as topical medicaments, and a deliberate effort has been made to correlate the laboratory and clinical results. In the vast majority of cases, it would seem that clinical results may be predicted with a reasonable degree of accuracy when the in vitro sensitivity of the organism is known. We have reported [5e] previously that neomycin used locally is superior to, or at least as effective as, any other available antibiotic for the treatment of cutaneous infections due to staphylococci and/or infections due to Gram-negative rods but that oxytetracycline and chlortetracycline are apt to be more effective in the vast majority of hemolytic streptococcus infections but not in all. It is our impression, and this is confirmed by our in vitro tests, that bacitracin may be very effective and definitely the antibiotic of choice for a significant percentage of hemolytic streptococcus infections; in other words, strains of hemolytic streptococci are either very sensitive to bacitracin or considerably less sensitive. We have had very little experience with the use of chloramphenicol and polymyxin topically, but in our hands chloramphenicol administered orally has been a very effective therapeutic agent for the systemic treatment of cutaneous pyogenic infections when systemic rather than local treatment is indicated. However, we consider penicillin administered parenterally or orally as the systemic antibiotic treatment of choice for acute staphylococcic and streptococcic cutaneous infections. In chronic skin infections, penicillin-resistant strains of hemolytic Staph. aureus are commoner; if systemic treatment is indicated for chronic bacterial infections of the skin, it is probable that chloramphenicol, oxytetracycline, or chlortetracycline will be more effective than penicillin because the bacterial organisms which are isolated under these circumstances are more likely to be sensitive to one or more of these broad-spectrum antibiotics which may be administered orally.

Rarely, chloramphenicol seems to cause serious potentially fatal hemopoietic reactions, and therefore we have discontinued systemic use of this antibiotic, because the risk, however small, does not seem justified. Furthermore, our data indicate that both oxytetracycline and chlortetracycline are apt to have a more pronounced in vitro effect for both hemolytic Staph. aureus and hemolytic Streptococci than chloramphenicol. It should be noted that nausea, vomiting, diarrhea, and proctitis may be observed following oral administration of all broad-spectrum antibiotics.

Our data do not make it possible for us to estimate the upper limit of sensitivity of a bacterial organism to a given antibiotic which is indicative of a sensitive versus a nonsensitive strain. We have the impression that an excellent result may be anticipated when the sensitivity is of the order of magnitude of 5 γ per milliliter or less. This may vary for different organisms and antibiotics. We have reason to believe that organisms sensitive to as much as 15 to 25 γ per milliliter (or higher) will respond to topical treatment satisfactorily. In many patients there seem to be a marked difference in response of the infection when aqueous solutions of the antibiotics are applied either as compresses or as soaks rather than in the form of ointments. We agree with Osborne [10] that compresses or soaks with aqueous solutions are to be more effective in the majority of patients, but this method of application is not feasible in many cases.

It is not necessary to emphasize that factors other than the in vitro activity are important in evaluating an antibiotic which is to be used for the topical treatment of cutaneous pyogenic infections. Experience to date indicates that the sensitizing potential of bacitracin, neomycin, chlortetracycline, and oxytetracycline is low. Indeed the percentage of sensitization reactions with neomycin and bacitracin is probably less than 0.5% ; the percentage of such reactions following topical application of chlortetracycline and oxytetracycline is slightly higher (0.5-1%). In experiments which will be reported later [21] we have found both neomycin and bacitracin to be unusually nontoxic for epithelial cells growing in tissue culture; in comparison chlortetracycline, oxytetracycline, chloramphenicol, tyrothricin, and especially gramicidin are at least several times more toxic for epithelial cells in tissue culture.

Neomycin is stable in aqueous solution and also thermostable, in contrast to other commonly used antibiotics (Table 16), and certainly this is a distinct advantage. Also residual bacterial counts, using the technique of Spicer,[22] indicate that neomycin is bactericidal as well as bacteriostatic in that with neomycin, the residual counts were zero or only a few organisms whereas with chlortetracycline, oxytetracycline, chloramphenicol, and bacitracin, the counts were seldom recorded as zero and in most cases they were very high. These findings may or may not be significant.

Cutaneous moniliasis at the site of application may occur as a complication of local therapy following the use of any of the broad-spectrum antibiotics.[13] It is probable that this complication can be prevented by the addition of a moniliastatic agent.

SUMMARY AND CONCLUSION

The in vitro sensitivity to neomycin of 377 strains of bacterial organisms isolated from cutaneous pyogenic infections has been determined.

The sensitivity to chlortetracycline (Aureomycin), oxytetracycline (Terramycin), chloramphenicol (Chloromycetin), and bacitracin to the majority of these 377 strains has been studied and compared in tabular form with the results which were obtained with neomycin.

These results indicate that both neomycin and oxytetracycline have a spectrum which includes both Gram-positive cocci and Gram-negative rods.

Chlortetracycline has an excellent spectrum for Gram-positive cocci but is much less active for Gram-negative rods than neomycin, oxytetracycline, and chloramphenicol. Chloramphenicol has a wide spectrum which includes both Gram-positive cocci and Gram-negative rods but is not quite as active against Gram-positive cocci as oxytetracycline and chlortetracycline. It appears that the incidence of side-effects with oral therapy is somewhat greater with chlortetracycline than with oxytetracycline. Neomycin is superior to all other antibiotics in regard to its in vitro effect on all strains of staphylococci. This antibiotic is not as active in vitro against hemolytic streptococci as oxytetracycline, chlortetracycline, bacitracin, and chloramphenicol, but about 40% of the strains which were tested were found to be sensitive to 6 mg. or less of neomycin per milliliter. Oxytetracycline is almost completely ineffective against Proteus. Bacitracin is effective in vitro against Gram-positive cocci but completely ineffective against Gram-negative rods. Its in vitro effect against Gram-positive cocci is exceeded by the broad-spectrum antibiotics.

The size of the inoculum influences the results of in vitro tests significantly.

In general, our clinical results with the topical use of neomycin, chlortetracycline, oxytetracycline, and bacitracin and with the oral administration of chloramphenicol parallel the in vitro results which are recorded in this report.

In addition to the antibacterial spectrum in the test tube, other factors, such as the irritant and/or sensitizing potential of the antibiotic as well as its stability and its solubility, influence the clinical effectiveness of the drug.

Additional prolonged clinical experience is essential before it will be possible to rate in order of preference the available antibiotics for topical use. It would seem that all the antibiotics which were included in this study have a place in our therapeutic armamentarium at the present time. No single antibiotic is the most effective one for every case. It is essential to do in vitro tests to select the antibiotic of choice for a given patient.

Because of its broad spectrum, solubility, stability, and apparent low potential for irritant and/or sensitization reactions, we consider neomycin sulphate a very effective, safe antibiotic for tropical use in the treatment of cutaneous pyogenic infections.

If it is not possible to do in vitro tests, on a percentage basis for topical therapy, it would seem advisable to select (in the order named) neomycin, oxytetracycline, chlortetracycline, and bacitracin for hemolytic Staph. aureus infections; chlortetracycline, oxytetracycline, bacitracin, and neomycin for hemolytic streptococci infections; and neomycin, oxytetracycline, and chlortetracycline for Gram-negative bacillary infection, although chlortetracycline is not very effective. Chloramphenicol and polymyxin B have been omitted from these selections because our experience with the topical use of these antibiotics has been limited. Polymyxin B is the most

effective for the topical treatment of Pseudomonas infections. Cutaneous moniliasis at the site of application has been mentioned as a possible complication of topical therapy with one of the broad-spectrum antibiotics.

ABSTRACT OF DISCUSSION

Dr. James W. Jordon, Buffalo: I am at the present time preparing a paper on the treatment of pyogenic infections of the skin. The purpose of the paper is to evaluate the use of antibiotic substances used topically in such conditions as impetigo, ecthyma, and so forth. I found from a clinical standpoint that nearly all the antibiotics were effective in the treatment of the common pyodermas. Differences in effectiveness clinically were minor with the exception of polymyxin, which is ineffective except in infection caused by Pyocyaneus groups of organisms.

There are other considerations, however, in the choice of antibotics for topical therapy. Among these are the sensitizing properties. With the exception of penicillin and streptomycin, the preparations do not appear to have a high sensitizing index. Another consideration is stability. Stable ointments can be prepared from all of them, but some of them deteriorate rapidly in aqueous solutions. If chlortetracycline, for example, is to be used in aqueous solution topically, fresh solutions must be prepared about every 48 hours.

In general, it is better to use as topical applications those antibiotics which cannot be used systemically, since if sensitization results from the topical use it will not deny the patient the later use of a medication which may be of extreme value in combating some future illness. An antibiotic which is colorless and does not stain the skin or hair obviously has certain advantages, since it is cosmetically acceptable to the patient. Dr. Livingood has shown that neomycin has the greatest in vitro bactericidal spectrum. In my experience clinically neomycin is very effective in the treatment of the common pyodermas. It is the most desirable antibotic for topical application from the standpoint of the other considerations that I have mentioned. It has a low sensitizing index, it is stable in aqueous solutions; it is not used systemically, and it is colorless. It is my opinion that neomycin most closely approaches the ideal antibiotic for topical use.

Dr. Ashton L. Welsh, Cincinnati: Dr. Livingood's presentation provides satisfying confirmation of the many existing reports of the in vitro activity of neomycin on bacteria isolated from pyogenic infections of the skin.

I should like to point out that studies of this type are best suited to the husbandry possible in institutional practice. They are impractical in the conduct of a private dermatological practice from the standpoint of economy, loss of time (in initiating effective therapy), inconvenience to the patient (who must visit a laboratory), and increased load on the physician (who must obtain materials for the laboratory).

If maximum information is to be obtained from in vitro studies, then these studies must be broadened to include: (1) differentiation between bacteriostatic and bactericidal activity; (2) determination of the zone of maximum activity. This is particularly true in the case of those antibiotics exhibiting toxic properties, such as neomycin, bacitracin, and polymyxin B.

Determination of the zone of maximum activity of these antibiotics might indicate use of a smaller concentration of these compounds, both topically and systemically. Johnson and Johnson (Johnson, C. W., and Johnson, T. W.: An in-Vitro Study of the Inhibitory Activity of Certain Antibiotics in Low and High Concentrations, *Antibiotics & Chemother.* 1: 560, 1951), employing several strains of bacteria found immediately below the lowest effective antibiotic concentration reported an area of decreased activity. At considerably lower antibiotic concentrations, areas of inhibition equal to those reported for much higher concentrations were observed. These investigators demonstrated this "paradoxical zone reaction" to be present in the case of neomycin. It remains to be determined whether this phenomenon is a property of specific bacterial groups or actually a property of the antibiotic itself.

Several investigators (Garrod, L. P.: The Action of Penicillin on Bacteria, Brit. M. J. **1**:107, 1945. Eagle, H.: A Paradoxical Zone Phenomenon in Bactericidal Action of Penicillin in Vitro, *Science* **107**:44, 1948. Jawetz, E.: Gunnison, J. B., and Coleman, V. R.: The Combined Action of Penicillin with Streptomycin or Chloromycetin on Enterococci in Vitro, ibid. **111**:254, 1950. Eagle, H., and Musselman, A. D.: The Slow Recovery of Bacteria from the Toxic Effects

of Penicillin, *J. Bact.* **58**:475, 1949. Mortara, F.; Feiner, R. R., and Levenkron, E.: Activity of Penicillin Against Hemophilus Ducreyi in Vitro, *Proc. Soc. Exper. Biol. & Med.* **56**:163, 1944) have shown by in vitro studies that high concentrations of some of the antibiotics are less actively bactericidal against certain strains of bacteria than lower concentrations of these compounds. The observations of these investigators suggest that inhibition of bacteria by antibiotics is not always a direct function of the concentration. Concentrations outside the optimal range may have either decreased activity or a stimulatory effect on the growth of micro-organisms.

The development of resistance to neomycin follows the pattern of penicillin.

I agree with Dr. Livingood that neomycin, because of the factors he listed, can be employed topically with effectiveness and safety in most pyogenic infections of the skin. I agree with him, also, that neomycin may be reasonably employed parenterally in those infections due to organisms proved by in vitro tests to be resistant to other less toxic antibiotics, provided neomycin is administered in small but frequent doses and for relatively short intervals.

In such cases, in vitro tests to determine possible zonal reaction with the particular bacteria involved might suggest use of doses of neomycin much lower than the recommended effective doses, thereby lessening the risk of toxic manifestations from parenteral administration.

In certain particular infections of the skin, I have employed neomycin alone as the second choice antibiotic for topical use. In intertriginous infections of all types (but particularly those occurring on macerated interdigital areas) I prefer polymyxin B in combination with penicillin or oxytetracycline. I adopted this approach because secondary moniliasis is not uncommonly a complication of bacterial infections in such areas, and neomycin seems, if anything, to further the moniliform complication.

In otitis externa, recent investigators report the presence of Pseudomonas aeruginosa in from 41 to 50% of the cases studied. (Hayes, M. B., and Hall, G. F.: The Management of Otogenic Infection, *Tr. Am. Acad. Ophth.* **51**:149, 1947. Salvin, S. B., and Lewis, M. L.: External Otitis, with Additional Studies on the Genus Pseudomonas, *J. Bact.* **51**:495, 1946. Gill, W. D., and Gill, E. K.: Otitis Externa: Some Comments Concerning Present Status of Therapy, *South. M. J.* **43**:428, 1950). Most of the other organisms found were bacteria and Candida (Monilia). In only 12.5% of cases were fungi found, and these were mixed with bacteria.

In view of the above, it seemed reasonable to employ a single antibiotic or a combination of antibiotics having a wide antibacterial spectrum with special activity against Pseudomonas. I have therefore used polymyxin B in combination with oxytetracycline, penicillin, chloramphenicol or neomycin. Results have been most satisfactory.

In children and infants I have used chloramphenicol eyedrops in the external ear canals because of ease of application.

In chronic infectious eczematoid dermatitis, hemolytic streptococci are found with regularity. Incidence percentage of this organism in various reports, including Dr. Livingood's (Livingood, C. S.: Nilasena, S.; King, W. C.; Stevenson, R. A., and Mullins, J. F.: Pyogenic Infections Treated with Neomycin, *J. A. M. A.* **148**:334, 1952), is approximately 30%. In addition, Proteus and Pseudomonas are commonly present.

Consequently, in chronic infectious eczematoid dermatitis I have used penicillin alone, one of the other broad-spectrum antibiotics alone, or combinations of the two, instead of neomycin alone.

I believe the ointment base employed for topical application of the antibiotics is important. Certain bases may, themselves, be sensitizing or irritating, or they may not release the antibiotic readily for penetration into infected tissue. I have found that such bases as combinations of water-miscible polyethylene glycol (carbowax) diesters, or combinations of polyethylene glycol with triethylamine are very satisfactory.

In conclusion, I believe neomycin is an excellent antibiotic agent for the topical treatment of infections of the skin. However, it has its limitations and does not replace other antibiotics in our armamentarium against skin infections.

DR. CLARENCE S. LIVINGOOD: I wish to thank Dr. Welsh and Dr. Jordan for their excellent discussion. It is agreed that the prolonged topical application of one of the broad-spectrum antibiotics may result in the development of localized cutaneous moniliasis at the site of application.

We were among the first to report this complication (*J. A. M. A.* **148**:334 [Feb. 2] 1952). As would be expected, it is more liable to occur when intertriginous sites are treated. Cutaneous moniliasis following topical treatment with the broad spectrum antibiotics may be prevented by the concomitant or alternate application of moniliastatic and/or moniliacidal drugs such as iodochlorhydroxyquin (Vioform). It is probable that this problem will be solved by the incorporation of an appropriate antifungal agent in the antibiotic ointment.

I agree with Dr. Jordon that the topical application of aqueous solutions of these antibotics may be more efficacious than the ointment preparation. However, it is not feasible to use compresses or soaks in all patients. It has been our experience that quite dilute aqueous solutions of these antibiotics may be effective; we have used aqueous solutions of neomycin containing as little as 500 γ per cubic centimeters and we are experimenting with even lower concentrations.

It seems mandatory to do in vitro tests if one is dealing with a chronic, well-established cutaneous bacterial infection which has not responded satisfactorily after the use of one or more of the available antibiotics. However, as Dr. Welsh has stated, it is not practical to do these involved expensive time-consuming in vitro tests routinely.

Information such as we have accumulated in this study makes it possible to select the antibiotic of choice for a given patient provided a bacterial culture has been done. It must be emphasized that a given antibiotic may be the most effective one for the particular patient in question, despite the fact that it is not the preferable one for the highest percentage of such infections.

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ASSOCIATION OF MUCOCUTANEOUS AND VISCERAL CANCERS

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PELLER * presented evidence in 1936 that the patient who had an epithelioma was less apt to develop a visceral cancer than the person with a normal skin. He based this conclusion on a study of the mortality statistics of England and Wales from 1921 to 1923. This so-called immunity persisted despite cure of the primary neoplasm. If this observation were true, it would suggest that epitheliomas could be produced by radiant, chemical, or mechanical means as a protection against malignant tumors with a poor prognosis. Peller went so far as to advocate this procedure, and *Lancet* published the suggestion. Being dissatisfied with the lukewarm reception to his idea, Peller has published a book claiming that cancer morbidity and mortality could be decreased by 90% by provoking early in life an epithelioma. One possible fallacy in this idea is to be found in Peller's concept that only 20% of the population is susceptible to cancer. However, it is impossible to state with certainty that a larger percentage would not develop cancer if they did not die of other causes. Peller minimized the cases in which an internal cancer was discovered after a superficial lesion by claiming that the former tumor may have been present at the time the latter was discovered. However, it is unlikely that the two neoplasms would have developed at the same time. Therefore, if one claims that one cancer protects against another, it should be recognized that visceral cancer failed to "immunize" against skin cancer in these cases. It is believed that deeper cancers develop oftener in patients with mucocutaneous growths than vice versa, because of the better prognosis for epitheliomas. One might also wonder why a keratosis, a recognized premalignant lesion and even considered to be a cancer in situ by many, does not offer the same immunity postulated by Peller. Every dermatologist realizes that one skin cancer does not protect against a second one.

Warren and various co-workers † reached a diametrically opposed conclusion. Employing cancer rates for normal populations as controls, these workers found that the patient with a skin cancer is more likely to develop a visceral cancer than is the person without such a neoplastic growth. In fact, Conrad and Hill [8] went so far as to reexamine Peller's own statistics and to show that Warren's viewpoint rather than that of Peller was the correct one.

From the Highland-Alameda County Hospital.

This study refers to independent cancers of the skin and internal organs and does not deal with metastatic lesions.

Read before the Section on Dermatology and Syphilology at the 102d Annual Meeting of the American Medical Association, New York, June 4, 1953.

* Footnotes 1, 2, and 3.

† Footnotes 4, 5, 6, and 7.

It is widely accepted that "figures do not lie." It is also granted that mathematics is an exact science. Yet, in attempting to adapt mathematical findings to medicine, an inexact science to say the least, we often overlook an important fact. In medicine, figures per se are meaningless. They are of significance only in comparison with other figures. In other words, a 75% cure rate for a given treatment of a certain disease can be evaluated only by comparison with the natural history of the disease and the prognosis when the disease is attacked by other therapeutic measures. Therefore, to establish a medical finding as a fact, one must employ controls.

Controls, too, are funny things. One cannot compare bananas with jet engines. Yet medical articles have been published with comparisons as absurd. By a judicious selection of controls, statistics can be used to prove anything. The answer to the question whether an epithelioma protects against or predisposes to internal cancer can be answered only by utilization of an adequate control. Unfortunately, adequate control is not as simple as it appears to be on the surface.

TABLE I.—*Findings in this Series*

Source	Cases of Epitheliomas	Association with Visceral Cancer	%
California Tumor Registry	3,000	180	5.9
Highland-Alameda County Hospital			
Active cases	464	14	3.1
Inactive cases	415	37	8.6
Total	879	51	5.8
Total	3,885	231	5.9

FINDINGS

Skin cancer constitutes an excellent tool for the study of multiple primary malignant tumors. The prognosis is good with modern destructive therapy. The patient lives long enough to develop an internal cancer if he has any tendency toward doing this.

Through the cooperation of Dr. James W. Ellis,‡ the findings of the California Tumor Registry were made available for this study. These comprise a summary of the data reported by 26 hospitals between 1942 and 1949. They include statistics on 3,006 persons who had one or more malignant cutaneous neoplasms. Of these patients, 180 (5.9%), were known to have developed one or more malignant neoplasms not affecting the skin; 1,246 (41.4%) patients had died at the time of the study. Only 22.6% of the latter were known to have had postmortem examinations.

Another fertile source of material was the Highland-Alameda County Hospital. A tumor board was established there in 1932 and has continued to date. Since this is the only free hospital in the immediate area, it afforded an excellent opportunity to follow the patients. An active follow-up system was combined with its geographic advantage. This hospital's statistics were included in the California Tumor Registry series only between 1946 and 1949, so that there was not a great deal of overlapping between the two series.

‡ Ellis, J. W.: Personal communication to the author.

From this source, 879 patients with histologically proved mucocutaneous malignant neoplasms were studied. Fifty-one of these patients developed visceral cancer simultaneously or chronologically in relation to their epitheliomas. They made up 5.8% of the entire group.

However, the figures were subdivided according to the charts in the active file and those in the inactive file. Of 464 patients with charts in the former category, only 14 (3.1%) were known to have suffered from internal cancers. In the inactive group, 415 records were studied, and 37 of the patients (8.6%) manifested visceral cancer sometime during the period of observation. This comparison indicates that the incidence increases with prolonged observation, since the rate was nearly three times as great in the old records as it was in the active cases. This observation is true despite improved methods of cancer therapy and greater survival rates and times. Also, it should be pointed out that even in the inactive series, only 212 (51.2%) were followed until death, and only about one patient in eight was examined on the autopsy table. In the California Tumor Registry series this figure was about 1 in 10. In other words, one must assume that the incidence would be higher if better opportunities existed for follow-up studies.

TABLE 2.—*Possible Control Series*

	Cases	Visceral Cancer	Per 100,000	%
Normal population rates				
45 to 64 yr	.....	.....	266.5	0.26
Over 65 yr	.....	.....	900.1	0.9
Lifetime expectancy				
Males	.....	.....	.....	14.79
Females	.....	.....	.....	20.43
Death statistics				
United States (1949)	1,443,607	190,895	.....	13.2
Over 45 yr	1,144,997	183,062	.....	16.0
Alameda county (1952)	7,391	1,149	.....	15.5
Highland-Alameda County Hospital	8,408	250	.....	2.9
Over 45 yr	2,766	250	.....	9.0

Other investigators have reported similar findings. For instance, Warren and Gates § noted an incidence of 6.7%; Burke,[9] of 7.8%, and Stalker, Phillips, and Pemberton,[10] of 8.4%.

CONTROLS

It must be reiterated that these findings are meaningless without proper controls. If one compares these figures with cancer rates for a normal population, neglecting Peller's 20% susceptibility rate, then it will be found that the patient with an epithelioma is at least six times as likely to develop an internal cancer as the person with an uninvolved skin. However, it should be recognized that here one is comparing a group of patients with skin cancer against another group consisting mainly of well persons. Secondly, one is comparing a group of patients in which nearly 40% have died against another group presumably still living. Third, the group with skin cancer has been studied over a period of time, while the population statistics are gathered at a given time. Fourth, it is impossible to state how many persons in a so-called normal population group have visceral cancers that have not been diagnosed or reported at the time the group is studied.

§ References 4 and 5.

Use of mortality statistics as a control establishes the opposite conclusion. In 1949 there were 1,443,607 deaths in the United States.[11] Excluding the lymphoblastomas and leukemias, there were 190,895 due to malignant growths. This figure represents 13.2% of all of the deaths. However, if one compares the statistics for the group who were more than 45 years of age, malignant tumors accounted for 16% of the deaths. Utilization of this control would suggest a lower incidence of visceral neoplasms in patients with superficial epitheliomas (6% vs. 16%). The difficulty in accepting these figures as a valid control lies in the fact that in the epithelioma series, more than 60% are living and still might develop visceral cancers, while all those in the "mortality series" have died and therefore have exhausted all possibility of developing such tumors.

Another possible control would be the lifetime expectancy figures. According to Levin,[12] 18.29% of men develop cancer sometime during their life. Elimination of cancer of the skin and lips and leukemia would leave 14.79% who would manifest malignant neoplasms. According to the same source, 22.22% of women suffer from malignant new growths, and 20.43% are deeper than the skin or mucous membranes of the oral cavity. These figures have the same weakness as the mortality statistics, precluding their acceptance as a valid control for this series.

TABLE 3.—*Histologic Types of Skin Cancer*

	Entire Series, %	Association of Cutaneous and Visceral Cancer, %
Basal-cell	50.0	51.7
Squamous-cell	39.8	43.7
Melanoma	10.3	4.6

The discharges from the Highland-Alameda County Hospital provided another possible control series studied. Use of this series eliminated many of the variable factors, including socioeconomic and geographic ones. Also, most of the persons comprising both groups were still living at the time of the study. Unfortunately, it did not overcome the objection that one is comparing a segment of the population at a given time against another group studied over a period of time.

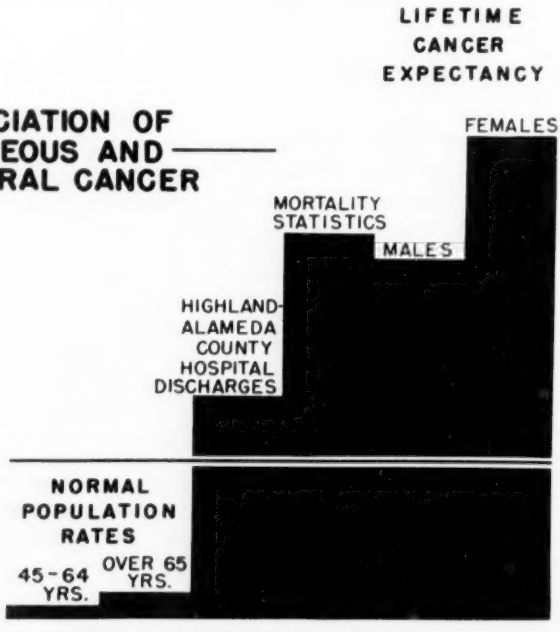
During seven months in 1952, 8,408 patients were discharged from the Highland-Alameda County Hospital or died there. Of these patients, 250 had visceral cancers. This figure represents 2.9% of the entire series. However, when one compares it with the 2,766 patients who were 45 years of age or older, 9.0% had internal cancer.

COMMENT

Certain facts are obvious. The longer a patient lives, the greater chance he has of suffering from a visceral cancer. The best method of diagnosing such a neoplasm would be autopsy. Since 60% or more of the 3,885 patients in this series are still living and only about 10% have had postmortem examinations, the reported 6% association with internal cancer must be a low one. No one can guess the actual percentage that occurs in persons with a history of superficial epitheliomas. However, studying the figures in this paper makes it seem likely that the incidence as shown by autopsy might approach that given in mortality statistics or in lifetime

expectancy figures. Actually a 6% incidence with 40% deaths would project to a 15% association in 100% fatalities, conforming to general mortality statistics. However, one can question the validity of such a straight-line projection.

This study did not reveal that any histologic type of mucocutaneous malignant tumor was more or less dangerous in this regard. The only exception to this observation was melanoma, which because of its disregard for age and poor prognosis was less often associated with internal cancer. Table 3 shows the incidence of the types of epithelioma in this series compared with the proportion of each in the group associated with internal cancer. Basosquamous-cell epitheliomas were included in



Summary of findings and controls.

the squamous-cell group. Statements cannot be made regarding the influence of various locations of internal or cutaneous neoplasms, because the distribution was so wide that the figures obtained were not significant.

No evidence was found to support the contention that the presence of multiple primary cancers improves the prognosis. In 37 fatal cases of associated mucocutaneous and internal cancer in the "closed file," death occurred in an average of 3.3 years after medical observation for the first malignant tumor.

This study did establish that internal cancer is not uncommon in patients with epitheliomas. It is questionable whether an incidence of even 6% could be construed as providing sufficient protection to warrant the production of skin cancer as a mechanism to immunize against visceral cancer.

Furthermore, even if Peller's choice of a control were applicable, one could not establish the presence of immunity by statistics. In other words, a survey might

demonstrate that redheads have more freckles than brunettes. However, that would not prove that one could prevent freckles by dyeing the infant's hair black. Therefore, his conception that visceral cancer can be prevented by the production of a superficial epithelioma cannot be proved by such statistical studies.

On the other hand, no definite evidence could be adduced to show that the presence of a cutaneous cancer predisposes to internal cancer. The only control that would suggest this theory is the least acceptable, statistically, of all those considered in this investigation.

SUMMARY

This paper is summarized by the accompanying chart. The horizontal line represents the known incidence of associated cutaneous and internal cancer (6%). As can be seen, this incidence is greater than that for normal population rates (0.2 to 0.9%) but less than that shown by mortality statistics (16%) and lifetime cancer expectancy figures (14.79% to 20.43%). It is also lower than that for the Highland-Alameda County Hospital discharges (9%). Therefore, the argument as to what effect mucocutaneous epitheliomas have on the incidence of visceral cancer can be established only by the selection of a proper control. If a large series of skin cancer cases were studied on the autopsy table, the resulting statistics could be compared with the mortality or lifetime expectancy rates and would be significant.

The facts presented in this paper suggest that, since most patients with mucocutaneous epitheliomas are in the cancer age and have a good prognosis, some of them will still develop internal cancer. It is possible that a large series of such patients subjected to postmortem studies might demonstrate that such superficial lesions have no effect on the incidence of visceral cancer.

ABSTRACT OF DISCUSSION

DR. ANTHONY C. CIPOLLARO, New York: Can a person be immunized against cancer? There have been articles published which would tend to indicate that a person with a cutaneous cancer is less apt to develop a more serious and a more malignant neoplasm of the viscera. Peller, especially, has shown evidence to indicate that a cutaneous neoplasm offers some protection against development of a more serious internal cancer. Others, for example Warren and Watson, believe and have published evidence that a cutaneous cancer makes one neither immune nor susceptible to a second cancer in the same or different organs. The evidence supporting both sides of the controversy is largely statistical and controversial. There is no published experimental evidence to support the advocates or the adversaries of the theory of immunity to cancer.

A detailed study of the various factors that influence the development of cancer leads me to believe that a person with skin cancer has no more and no less chance of developing cancer of the viscera than a normal person. There is no constitutional predisposition to multiple cancers of different organs, and by the same token, there is no immunity conferred by the first cancer. Excluding metastases, each cancer that develops in the same person is new and independent of any cancer developing subsequently to the first one. There are some exceptions, as in the case of multiple arsenical cancers, tar cancers, and radiodermatitis. The same generic organ might show a predisposition to multiple cancers. The best argument against the concept that cancer of the skin makes one less susceptible to cancer of the viscera is the published evidence of cases of cancer of the lip, thyroid, breast, lungs, stomach, and genitourinary system in patients who had cutaneous neoplasms. Even lymphomas have occurred in patients with epidermoid carcinomas.

In masterly statistical fashion from material available to him, Dr. Epstein has shown the difficulty of proving unequivocally that a first cancer confers some protection against the development of a second cancer. In fact, he has emphasized the difficulties of drawing conclusions from comparative statistics based on control groups. His statistics justify his conclusion, with which I agree, that an epithelioma of the skin neither protects against nor makes one more susceptible to more serious visceral cancers.

DR. SIGISMUND PELLER, New York: I am indebted to Dr. Epstein for the discussion of cancer immunity. I devoted to this problem about half of my life and a book of almost 600 pages, "Cancer in Man," published a few months ago. There the methods of studying immunity are dealt with in 2 out of 20 chapters.

In studying cancer immunity, we are about as far as bacteriology was prior to Koch. We have established principles of working. But it is not only a matter of statistics; diagnosis and histology also have their pitfalls. If only one statistical method is used, the results may not be reliable. Therefore I try out three methods. If all three of them yield the same result, then it is correct. If one of them leads to a divergent result, then the reliability of this or of all three methods has to be reexamined.

In the first method multiple cancers are divided into simultaneous and metachronous. To base discussion of immunity on simultaneous multiple cancers is like inoculating a case of primary chancre with syphilis. He will develop a secondary primary chancre. If, however, a person has had an untreated chancre for months, attempts to reinfect him remain unsuccessful.

For the study of cancer immunity, only metachronous multiple cancers should be used. The disease must reach a certain stage before it has produced enough immunization bodies. I do not know whether the process is serological or cytological. Because of immunity, metachronous tumors are rare.

The second method is that of studying longevity. I found the life expectancy of skin cancer patients to surpass that of the average. The reason is that in the former internal primary cancer develops less often than in other cancer-disposed persons.

The third method is that of cancer surveys of groups exposed to additional cancerogenic irritation of various kinds. I found a changed distribution of primary cancers, an increased incidence for the strongly exposed organ, and a diminished cancer frequency for organs which were not additionally exposed. Without immunity, this situation would be impossible. All three methods demonstrated that cancer of the skin and lips immunizes against internal cancer.

Dr. Epstein should publish his data in as much detail as possible. I will then analyze his material and use it for a demonstration of methodology I consider proper.

DR. A. J. REICHES, St. Louis: I have no simple answer to the problem. It is evident that accurate statistical information regarding precancerous and cancerous cutaneous conditions is needed. At the St. Louis City Infirmary Hospital, about two out of every three persons over 60 have senile keratoses. Textbook quotations that 15, 20, or 25% of persons who have senile keratosis will probably develop cutaneous carcinoma should be checked with actual statistical studies.

I do hope that public health reports on the percentage of cutaneous carcinoma will be based entirely on biopsy and not on clinical diagnosis. For example, public health reports on the high percentage of cutaneous carcinoma in Denver and the comparatively low percentage in Chicago, in my opinion, need to be reappraised. Accurate information about cutaneous carcinoma is a necessity before one is able to evaluate the possibility which Dr. Epstein has discussed in his paper.

DR. ERVIN EPSTEIN, Oakland, Calif.: It was very gratifying to have Dr. Peller discuss my paper. However, as indicated by the tone of my presentation, I am not in complete agreement with him. One could discuss each point that Dr. Peller raised, but most of them are answered in the body of the paper. The question of low incidence of internal cancers in the South, however, is worthy of comment. I am not acquainted with the incidence of visceral cancer in this portion of the country but for the sake of argument am willing to accept Dr. Peller's statement that it is lower. I am also willing to grant that there is more sunshine in the southern states and that sunshine is a potent factor in the production of epitheliomas. But Dr. Peller has failed to recognize that the cutaneous carcinogenic effect of solar radiation differs in various persons. For instance, the Negro has little tendency to develop skin cancer. Obviously, the proportion of Negroes is high in the South. Therefore, if one takes population figures which include all races and cutaneous colors, one has not established that there is an increased incidence of epitheliomas in this part of the country, which has an abundance of sunshine. In other words, the mere fact that there is more sunshine in one part of the world does not necessarily mean that there is more skin cancer.

The point regarding an internal cancer that is discovered soon after an epithelioma is well taken. However, in my series the occurrence of internal cancer months or years after an epithelioma was not unusual. In some instances, there was a difference of as much as 10 years. Obviously, this period was shorter in most instances because the patient was in the "cancer age" when he developed his first neoplasm.

As far as various experimental studies on animals showing that skin cancer protects against an internal cancer are concerned, human beings are not rats. Neither are induced and spontaneous malignant tumors identical. I feel that this problem can be evaluated for human beings statistically only. Figures do not lie, but interpretation of mathematical facts may lead to erroneous conclusions. From the utilization of a battery of controls in my work, it seems likely that in the genus Homo sapiens cutaneous cancers do not protect against or predispose to independent spontaneous visceral cancer.

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TREATMENT OF PEMPHIGUS WITH CORTISONE BY MOUTH

ADOLPH H. CONRAD Jr., M.D.
JEROME GREENHOUSE, M.D.
AND
RICHARD S. WEISS, M.D.
ST. LOUIS

WHEN CORTISONE for oral administration became available, the manufacturer placed at our disposal a large supply of the drug for use in the treatment of pemphigus. During the period covered by this report, eight cases were available, five of pemphigus vulgaris, two of pemphigus erythematosus, and one of pemphigus foliaceus.

An attempt was made to follow the laboratory work-up so as to provide a comparison with the laboratory results obtained when cortisone was given by the parenteral route. These results are in the accompanying Table.

REPORT OF CASES

CASE 1.—*History.*—Mrs. J. T., a white woman aged 48, was in good health until November, 1949, at which time fever, coryza, and a sore throat developed. She then noticed a white patch on the side of the tongue about the size of a quarter. She was told by her local physician that she had a similar patch in her throat and that it was a fungous infection. From that time until February, 1950, she had attacks of hoarseness, which persisted. She received treatment with penicillin and streptomycin, with some improvement in her symptoms. During this period, occasional sores would develop in her mouth and on her lips. About five weeks prior to her admission to Barnes Hospital (Sept. 16, 1950) lesions began to appear on her face. At that time Candida (Monilia) albicans was cultured from the mouth lesions. Three weeks prior to admission, the skin became involved in a generalized eruption which was vesicopapular in type with some large bullae.

Physical Examination.—Physical examination revealed a 48-year-old moderately obese white woman, with extensive and classic skin lesions of pemphigus vulgaris. There were also lesions of the buccal mucous membranes and of the vulvae.

Laboratory Data.—Total eosinophile counts were, unfortunately, not determined. There was very mild secondary anemia. The differential cell counts were not significant, except for 14% eosinophiles on one occasion. Total protein level was normal, but the albumin : globulin ratio approached 1 : 1 on one occasion. The sedimentation rate was elevated. A minor degree of liver damage was indicated by the cephalin-cholesterol flocculation test. Results of blood chemistry studies were apparently within normal limits. No urinary abnormalities were noted (Table).

Studies, observations, and reports from the Dermatological Department of the Barnard Free Skin and Cancer Hospital, the Division of Dermatology, Department of Medicine, Washington University School of Medicine, and the Barnes Hospital.

Read before the Section on Dermatology and Syphilology at the One Hundred First Annual Session of the American Medical Association, Chicago, June 11, 1952.

Merck & Company, Inc. provided their product, Cortone, in an amount sufficient to treat the patients reported here.

Blood and Urine Studies of Cortisone-Treated Patients with Pemphigus

	Blood Studies																									Urine Studies		
	Chambers Eosinophile Count	RBC, Million	Hb, Gm.	WBC	Platelets	Stab Forms, %	Seg. Forms, %	Eos., %	Lymphocytes, %	Monocytes, %	Total Protein, Gm.	Albumin, Gm.	Globulin, Gm.	Sed. Rate, Mm./Hr.	NPN, Mg.	Cephalin Flocculation	Thymol Turbidity	Fast. Blood Sugar, Mg.	Uric Acid, Mg.	Creatine, Mg.	Chloride, Mg.	P, Mg.	Ca, Mg.	K, Mg.	Na, Mg.	Specific Gravity	Albumin	Sugar
Case 1																												
9/16/50	...	4.08	11.9	12,200	.....	5	54	3	32	5	7	5.8	1.2	46	13	1+	.....	85	...	...	...	...	....	...	...	1.028	Neg.	Neg.
10/10/50	...	4.25	12	9,500	.....	2	64	14	17	3	5.5	2.8	2.7	..	22	...	.....	79	...	...	110	...	15.2	4.93	...	.....	.....	.....
Case 2																												
12/ 7/50	...	3.84	10.8	9,350	368,640	2	49	5	40	4	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
9/ 5/51	311	4.37	12.6	10,500	.....	..	66	1	20	3	...	...	...	49	11	...	.....	73	...	...	101	...	....	...	...	1.006	Trace	Neg.
																								(9/9/51)		1.011	2+	2+
Case 3																												
7/14/51	400	3.66	12	8,250	.....	4	53	5	38	..	4.8	2.3	2.5	..	26	...	.....	74	1.5	1.35	412	2.8	....	9	...	.....	.....	.....
7/18/51	221	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	1.026	Trace	Trace
7/20/51	236	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
7/25/51	300	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
8/ 4/51	35	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
Case 4																												
7/ 3/51	200	4.78	11	9,450	.....	..	72	3	19	..	5.8	3.45	2.35	..	33	...	.....	92	2.73	1.3	472	1.9	15.85	...	...	.....	Neg.	Neg.
7/17/51	100	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	509	...	....	...	...	.....	.....	.....
7/20/51	200	4.25	11	9,600	.....	1	75	2	19	..	...	...	...	..	..	...	.....	88	...	...	450	...	....	...	...	.....	.....	.....
Case 5																												
9/14/51	263	3.2	11	6,600	.....	2	46	10	37	5	5.8	3.95	1.85	..	25	...	.....	88	1.76	1.7	412	4.75	18.2	...	...	.....	Neg.	Neg.
9/21/51	393	....	....	.....	.....	..	..	..	..	..	5.45	3.45	2.0	..	36	...	.....	92	...	...	450	2.85	16.3	...	...	.....	.....	.....
Case 6																												
8/30/51	...	5.2	17	10,650	Normal	5	63	3	29	0	6.5	4	2.5	16	20	...	6.8 units	74	...	...	...	...	....	...	...	1.030	Trace	3+
5/28/51	88	5.0	15.6	11,400	.....	8	62	1	23	4	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	1.012	Neg.	Neg.
8/30/51	...	4.87	13.9	.....	.....	5	62	3	27	3	8.8	4.5	4.3	..	20	...	.....	121	...	...	98	...	....	4.3	148.6	1.020	Neg.	Neg.
9/11/51	...	....	18.3	12,500	.....	..	94	..	5	1	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
12/29/51	...	4.75	14.3	7,800	.....	..	72	2	26	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	1.024	Neg.	Neg.
1/10/52	286	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....

Case 7																											
7/23/51	1,950	5.13	14	18,000	Adequate	7	75	7	6	3	5.7	3.6	2.1	..	22	...	.....	107	...	...	98	...	....	4.3	144	1.025	0	0
7/31/51	1,651	4.85	14.5	15,800	.....	12	69	..	16	3	...	...	...	..	19	...	.....	81	...	...	102	...	....	...	145	.....	.....	.....
8/ 1/51	502	....	....	.....	.....	..	..	..	..	..	...	...	...	..	24	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
8/ 3/51	264	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	111	...	...	97	...	....	...	144	.....	.....	.....
8/ 4/51	142	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
8/ 7/51	33	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
8/11/51	44	4.48	12.5	21,200	.....	8	66	..	26	..	...	...	...	..	22	...	.....	86	...	...	...	...	....	...	...	1.012	0	0
8/15/51	33	....	....	.....	.....	..	..	..	..	..	...	...	...	..	13	...	.....	86	...	...	110	...	....	4.4	148	.....	.....	.....
8/17/51	44	....	....	.....	.....	..	..	..	..	..	...	...	...	..	17	...	.....	52	...	...	104	...	....	4.7	152	.....	.....	.....
8/26/51	242	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
9/ 4/51	176	....	....	.....	.....	..	..	..	..	..	...	...	...	..	24	...	.....	66	...	...	102	...	....	5.0	147	.....	.....	.....
1/23/52	122	5.1	15	.....	.....	6	77	5	8	4	5.6	3.6	2	11	24	...	.....	95	...	...	98	...	....	5.6	137	1.020	Trace	0
1/28/52	55	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
2/20/52	...	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	232	...	...	...	...	....	...	...	.....	1+	4+
Case 8																											
5/31/51	660	5.09	16	10,500	.....	2	69	3	21	5	...	...	...	26	..	...	.....	..	...	...	...	...	....	...	...	1.029	0	0
6/ 2/51	110	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	79	...	...	95	...	....	3.8	140	.....	.....	.....
6/25/51	156	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	84	...	...	...	...	....	3.7	138	.....	.....	.....
7/ 2/51	...	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	69	...	...	...	...	....	3.3	131	.....	.....	.....
7/ 5/51	...	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	92	...	...	...	...	....	4.2	144	.....	.....	.....
7/10/51	...	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	81	...	...	...	...	....	3.8	147	.....	0	0
7/18/51	...	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	70	...	...	...	...	....	4.3	153	.....	.....	.....
7/20/51	171	4.36	14	13,200	.....	8	70	..	16	6	...	...	...	..	..	...	.....	111	...	...	...	...	....	3.9	144	.....	.....	.....
8/10/51	110	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	70	...	...	...	...	....	4.0	148	.....	.....	.....
9/ 1/51	...	....	15.1	.....	11,600	..	..	..	..	..	...	...	...	..	24	...	.....	86	...	...	...	...	....	3.7	150	.....	.....	.....
11/26/51	280	4.3	13	11,250	.....	5	61	2	25	5	6.2	3.7	2.5	..	24	...	.....	81	3.93	2.1	578	...	11.75	3.95	152	.....	0	0
11/28/51	302	....	....	.....	.....	..	..	..	..	..	...	...	...	..	..	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....
12/14/51	415	....	....	.....	.....	..	..	..	..	..	3.05	1.7	1.35	..	39	...	.....	..	3.78	2.4	558	...	....	...	...	.....	.....	.....
1/10/52	...	....	....	.....	.....	..	..	..	..	..	...	...	...	..	50	...	.....	..	...	...	...	...	....	...	...	.....	.....	.....

Hospital Course.—A soft diet was prescribed for the patient. Bismuth tribromophenate (Xeroform) ointment was applied to the lesions, and the eyes were treated with a solution of boric acid. Corticotropin (ACTH) therapy was started, but there was no response after three days of treatment and so she was given sodium cacodylate by intramuscular injection for a few days. She grew steadily worse, and use of corticotropin was reinstituted, with no benefit. Finally, parenteral administration of cortisone was started, and there was steady improvement up to the time of the patient's discharge on Dec. 12, 1950. The dose of cortisone began with 200 mg. on Oct. 9, 1950, and this was increased gradually up to 300 mg. daily on Oct. 24. It was then reduced slowly until the patient's discharge on Dec. 12, at which time she was taking 150 mg. and the skin lesions were practically cleared.

After her discharge from Barnes Hospital, she was given 15 mg. of cortisone every second day. She also received 250 mg. of ascorbic acid three times daily. On Jan. 15, 1951, there had been no fresh lesions, and the cortisone dosage was reduced to 15 mg. every three days. On Feb. 6, the patient was given oral cortisone and was instructed to take one 25 mg. tablet every third day. On Feb. 19, there were one or two erosions in the mouth and no outbreak on the skin. The patient was seen again on March 26, at which time her skin was clear. On May 28, she had one lesion in the mouth and one lesion on the neck. The dosage was increased to one 25 mg. tablet every six hours for eight doses; then one tablet was given every other day. The patient was seen again on Aug. 13, at which time she had one lesion on the tongue, one lesion on the left side of the neck, and one lesion on the right side of the nose. The dosage was increased to one tablet daily for two weeks, and then it was reduced to one tablet every second day.

Case 2.—Mr. E. R., a white man aged 60, was first seen as an outpatient on Feb. 22, 1950, at which time he presented a generalized bullous eruption, which appeared to be erythema multiforme, and he showed some improvement with treatment with sodium salicylate.

However, on June 21, 1950, he entered Barnes Hospital with an extremely severe generalized eruption characteristic of pemphigus vulgaris.

During this stay in Barnes Hospital, he was treated with corticotropin and given sodium cacodylate intramuscularly. There was definite improvement, but on Sept. 13 more lesions appeared and it was noted that this seemed to be a treatment failure as far as corticotropin was concerned. The patient was discharged from the hospital and treated as an outpatient with arsenicals, with considerable improvement. On Dec. 12 he was free of lesions, but on Dec. 22 new bullae began to appear on the right leg. These subsided, and he remained relatively free of symptoms. He then went to Florida for a vacation. He returned on May 23 with a vesicular rash on the wrist, forearms, and right eyelid, which was diagnosed as dermatitis venenata. When he was seen on June 20, the areas where this vesicular eruption had appeared now presented lesions which were again characteristic of pemphigus. He was given cortisone by mouth at home and when seen on June 27 was greatly improved. The dose was 100 mg. daily. This was reduced gradually, and sodium cacodylate was given by intramuscular injection as the dose was decreased. On August 30 new lesions of pemphigus appeared and the same treatment was continued, but the patient gradually became worse.

On September 5, he was readmitted to Barnes Hospital, with many new lesions, and was given 100 mg. of cortisone by mouth; this dose was increased on the second day to 300 mg. and then gradually reduced to 100 mg. every second day. On Sept. 11, the patient was discharged from the hospital, with no active lesions.

On both hospital admissions the laboratory work-up was not notable. The one total eosinophile count done was 311. The red and white blood cell and differential counts were within normal limits, as were results of the blood chemistry studies. The sedimentation rate was elevated. Urinalysis revealed 2 + reaction for albumin and 2 + for sugar (Table).

Case 3.—Mrs. J. S., a white woman aged 69, was first seen as an outpatient on Aug. 18, 1948. At that time, she presented a generalized vesicular eruption which apparently was erythema multiforme.

She was treated with parenteral injections of penicillin and sulfapyridine by mouth, with gradual improvement, remaining well until June 18, 1949. At that time, she had groups of excoriated vesicles on the legs, which gradually spread despite all treatment with antibiotics, antihistamines, and salicylates.

A diagnosis of pemphigus vulgaris was then made, and a biopsy was done; it confirmed the clinical impression. Treatment with potassium arsenite solution induced a remission, but the eruption recurred. The patient was next treated with ferric cacodylate intravenously, with little or no benefit.

She entered St. Mary's Hospital in East St. Louis, Ill., and was treated with cortisone parenterally, with some improvement.

On July 14, 1951, she was again admitted to St. Mary's Hospital and presented a tremendously profuse eruption which was characteristic of pemphigus foliaceus.

A chest x-ray revealed bilateral pulmonary emphysema, with cardiac enlargement to the right and to the left. The basal metabolic rate was + 48%. The rest of the laboratory work-up was not notable. The total eosinophile count showed a fall from 400 to 35 over a period of one month. There was a very mild secondary anemia, with normal white blood cell and differnetial counts. Total proteins were below normal, and the albumin: globulin ratio was 1:1. There was a lowered potassium and phosphorus content, but results of the rest of the blood chemistry studies were normal. There was a trace of both sugar and albumin in the urine (Table).

The patient was treated with cortisone by mouth, beginning with a dose of 300 mg. daily and in a week or two raising the amount to 600 mg. This was reduced after about a week to 200 mg. daily.

With this treatment there was no noticeable improvement, and the cortisone therapy was stopped.

Case 4.—*History.*—Mrs. F. L., a white woman aged 39, entered the Barnard Free Skin and Cancer Hospital on June 27, 1951. She complained of an eruption of blisters, which had begun about six months previously on the chest and finally spread all over the trunk, with lesions on the scalp, on the perineum, and in the mouth. There was no loss of weight or associated complaints, except headache and fatigue. There had been no previous similar complaints, or previous treatment.

Physical Examination.—All the eruption was around the midline of the chest, epigastrium, and midline of the back and consisted of bullae and vesicles, apparently arising on nonerythematous bases, erupting and crusting. A diagnosis of pemphigus erythematosus (Senear-Usher syndrome) was made.

Laboratory Data.—The total eosinophile counts were 200, 100, and 200, respectively, within a period of two and a half weeks. The red and white blood cell and differential counts were normal. The total protein level and the albumin: globulin ratio were approximately normal. The phosphorus content of the blood was lowered, while the calcium was elevated, and the rest of the blood chemistry was normal. No urinary abnormalities were noted (Table).

Hospital Course.—The patient was given cortisone by mouth, 300 mg. daily on June 30, reduced to 100 mg. twice daily on July 1, and 50 mg. twice daily on July 2. This dosage was raised on July 4 to 100 mg. twice daily and on July 13 to 100 mg. three times daily. It was then noted that the lesions on the mouth and scalp had healed, but the ones on the trunk were still present and were oozing and crusting. On July 18, the oral cortisone dose was raised to 400 mg. daily, reduced to 300 mg. on July 19, and raised to 600 mg. on July 20. From July 21 through July 23 the patient was given 300 mg. a day. On July 24, she was placed on a schedule of 600 mg. a day, and it was then noted that there was no change in the lesions. From then on, she was treated with 400 mg. a day up to July 31. Then the dose was reduced to 100 mg. daily. She was discharged on Aug. 1, with many lesions still on the trunk, still oozing and crusted, but with no new bullae having formed.

Since her discharge, the patient's condition has been followed in the clinic and she has received arsenical therapy in the form of potassium arsenite (Fowler's) solution. When last seen, she still showed lesions on the trunk and occasionally a new bulla on her chest.

Case 5.—Mrs. A. H., a Negro woman aged 33, was seen for the first time at the Barnard Free Skin and Cancer Hospital on Aug. 6, 1951. She reported in the history that three months previously small blisters had developed on the chest. At that time, she was found to have crusted lesions involving the face in a butterfly distribution and the exposed areas of the chest and back. One bulla was found on the chest.

A diagnosis of pemphigus erythematosus (Senear-Usher syndrome) was made.

She made no improvement after parenteral treatment with penicillin and oxytetracycline (Terramycin) ointment administered locally. In fact, the lesions continued to increase in number, and on Aug. 24, potassium arsenite solution was prescribed; slight improvement occurred.

The patient was admitted to the hospital on Sept. 7. The laboratory work-up was not notable. The eosinophile response to the Thorne test was negligible. The total eosinophile count rose from 263 to 393 in one week. There was a very mild secondary anemia, but the white blood cell and differential counts were within normal limits. The total protein level and the albumin: globulin ratio were also normal. The calcium was elevated on two occasions, but the rest of the blood chemistry studies were within normal limits. No urinary abnormalities were noted (Table).

Therapy was then changed to cortisone by mouth, beginning with 300 mg. in divided doses daily. This administration was started on Sept. 18. Since no improvement was noted, the dose was raised to 600 mg. on Sept. 21, reduced to 400 mg. on Sept. 23, and to 300 mg. on Sept. 25.

At this point the patient's face had become very full, and the thighs and abdomen were edematous. She had a severe headache, and the blood pressure had increased from 106/76 to 140/100. On Sept. 26 the cortisone dose was reduced to 100 mg. daily, given until Sept. 27. During this period the patient gained about 12 lb. (5.4 kg.), losing 6 lb. (2.7 kg.) when the cortisone dosage was reduced. The cortisone therapy was stopped, and the patient was discharged from the hospital, the skin lesions having almost completely healed.

Case 6.—Mr. J. L., a white man aged 58, was first seen in Barnes Hospital on March 29, 1951. He had a 10-year history of migrating polyarthritis, with residual deformity of the elbows, shoulders, and ribs. Before this, he had been treated with parenterally administered cortisone and vitamins, with some improvement.

Five months prior to his entering the hospital, a generalized vesicular eruption developed, the vesicles containing clear fluid, and this condition, in spite of treatment by his local physician, continued to progress.

On entering the hospital, he presented a generalized eruption, characteristic of pemphigus foliaceus, extremely severe and generalized.

His physical examination revealed normal vital signs, and the joint changes were compatible with rheumatoid arthritis.

The laboratory data on admission were essentially normal. The total eosinophile counts were all within normal limits, as was the total protein level and the albumin: globulin ratio. were all within normal limits, as was the total protein level and the albumin: globulin ratio. The blood chemistry values were apparently within normal limits, except for a slightly lowered sodium content. There was a 3 + reaction for sugar on the first urinalysis, but the reactions for albumin and sugar were negative on three successive urinalyses (Table).

On his first admission to the hospital, the patient was treated with parenteral injections of cortisone in the standard dosage and was discharged from the hospital on June 1, with the lesions completely cleared up.

On Aug. 30, 1951, the patient was readmitted to the hospital, and this time he had a generalized eruption of pemphigus vulgaris, with scattered 1 to 3 cm. bullae over the entire skin.

Treatment was then started with cortisone by mouth, beginning with 100 mg. daily in divided doses. This was increased to 600 mg. and then reduced to 150 mg. The result was that all his lesions, except two or three stubborn ones, cleared up. Then, in addition to the cortisone, he was given a daily intramuscular injection of 200 mg. of heparin sodium (Depo-Heparin [1]). Rapid improvement resulted, and the patient was discharged on Sept. 28, all his lesions having cleared up, and his local physician was instructed to keep him on a regimen of 100 mg. of cortisone daily and 200 mg. of heparin three times weekly.

Cortisone therapy was stopped on Nov. 20, 1951, because of rise in blood pressure. Two weeks later, the patient was again given cortisone for his arthritis, but he discontinued the therapy and his skin lesions recurred. He was readmitted to Barnes Hospital on Nov. 30, 1951, with scattered bullae on the trunk. He was treated with corticotropin by intravenous drip, with very little improvement. Oral cortisone therapy was started on Jan. 15, 1952, but was changed to a suspension of corticotropin (Acthar-Gel) on Jan. 17, 1952, and the skin lesions improved materially, and the hormone medication was stopped. The patient was given nitrogen mustard

(methyl-*bis* or *tris* [B-chloroethyl]-amine hydrochloride) from Jan. 26, to Feb. 2 for his arthritis, and, very surprisingly his skin lesions had cleared entirely at the time of discharge, on Feb. 7.

Case 7.—Mrs. P. E., a white woman aged 67, entered Barnes Hospital on July 23, 1951, with a history that her present disease began with a sore throat in 1950, followed by blisters in her throat and mouth. Under treatment by her local physician, she received no relief. In January, 1951, blisters appeared on her feet and gradually spread to cover the entire skin.

Physical examination revealed an extremely profuse eruption of pemphigus chronicus vulgaris.

Cortisone therapy was started, 300 mg. daily in divided doses, on Aug. 4, 1951. The dosage was reduced to 200 mg. on Aug. 8, and 100 mg. on Aug. 23, this dosage being maintained until her discharge. A 2 gm.-salt diet was prescribed during this period.

The laboratory work-up was not notable, although there were a few white and red blood cells in the urine. The total eosinophile count showed a steady decline from 1,950 to 55 over a period of six months. The white blood cell count was slightly elevated, with a predominance of polymorphonuclear forms. The blood sugar rose to 232 mg. per 100 ml. at the time of onset of mild diabetes induced by huge doses of cortisone. The rest of the blood chemistry values were essentially normal. The urine showed a reaction of 1 + for albumin and 4 + for sugar at the time when huge doses of cortisone were being used (Table).

There were no notable side-effects from the cortisone therapy, and there was a slow steady improvement of the skin lesions until they had completely disappeared when she was discharged, on Sept. 29.

Her skin remained clear until Jan. 1, 1952, when there was an exacerbation of the skin lesions following an upper respiratory infection, and she was readmitted to Barnes Hospital on Jan. 20, 1952. The course was down-hill, and she became critically ill. She was given 200 mg. of cortisone, then 600 mg., and then 900 mg. daily together with 1½ grains 0.09 gm. of thyroid, and, finally, the lesions began to clear, on Feb. 9, 1952. The dosage was then lowered to 600 mg. of cortisone on Feb. 26, and then to 400 mg.; the patient has continued to improve up to the present time (March, 1952).

Case 8.—Mr. P. H., a white man aged 43, entered Barnes Hospital May 17, 1951. He complained of a generalized skin eruption, which he stated had begun about a year previous to entry. It had begun with ulcerations in the mouth. Three weeks previous to his entering the hospital, an eruption appeared all over the body, including the penis and scrotum. He was treated by his local physician with chlortetracycline (Aureomycin), both locally and systemically, with no result.

On examination, he presented a very profuse bullous and crusted eruption involving the entire skin, with marked involvement of the buccal mucous membrane and the face.

Findings on laboratory examinations at the time of admission were not notable. The Nikolsky sign was positive. The total eosinophile count fell from 660 to 110 over a period of three months, only to rise again to 415 within the next three months. The red and white blood cell and differential counts were essentially within normal limits. The total protein level was lowered, and the albumin : globulin ratio approached 1 : 1 terminally, while the sedimentation rate was elevated at the same time. The rest of the blood chemistry values were apparently within normal limits. No urinary abnormalities were noted (Table).

Oral cortisone therapy was started on July 6, with a 2 gm.-salt diet. The cortisone dose was started at 600 mg. per day and then was reduced in a few days to 300 mg. With the administration of the 600 mg. dose he made considerable improvement, but he began to relapse when the 300 mg. dose was used. The dose was raised again to 600 mg. daily for a few days and then was reduced to 250 mg. daily. With this therapy, the patient's lesions slowly and steadily healed, leaving dark pigmented areas where each one had involuted. On Oct. 3, there were only a few active lesions about the neck and axillae and the patient was very comfortable.

All the laboratory findings were within normal limits (Table), and there were no serious side-effects. Occasionally there was a slight edema of the legs, and occasionally slight puffiness about the face was noted. At the time of discharge, on Oct. 16, 1951, the patient still had lesions on his nose and on the back of his neck. His condition was followed in the outpatient clinic, and he continued to take 150 mg. of cortisone daily until Nov. 1, 1951. New blisters developed despite continuation of the cortisone therapy.

The patient was admitted to the Barnard Free Skin and Cancer Hospital on Nov. 25, 1951, and despite the use of oral cortisone in high dosage combined with penicillin and oxytetracycline his condition continued to deteriorate. Corticotropin heparin, and sodium arsenate had no effect on the course of the disease, and the patient died on Jan. 23, 1952, at which time he was covered with large bullae and denuded areas.

The autopsy showed lipid depletion of the adrenals, the cells in the cortex containing almost no lipid vacuoles. Also, there were spaces between the cells suggesting tubules, and these are qualitatively the same changes as those designated as pseudotubular degeneration. There was also a necrotizing esophagitis, but the inflammatory reaction in the esophagus showed only a slight amount of granulation tissue. The lower lobe of each lung revealed a necrotizing bronchopneumonia with relatively little inflammatory response. These changes are consistent with the morphologic responses to corticotropin and cortisone administration.

SUMMARY OF CASES

Case 1 was a case of pemphigus vulgaris showing no response to corticotropin (ACTH) therapy. With oral cortisone therapy the eruption cleared up almost entirely.

Case 2 was a case of pemphigus vulgaris which was a treatment failure with corticotropin. With oral cortisone therapy the eruptive phenomena of the disease were controlled, and the patient's general condition now is good.

Case 3 was a case of pemphigus foliaceus in which treatment with cortisone by mouth produced little or no effect. It is possible that if the cortisone therapy had been advanced to a higher dosage some results might have been obtained, but the patient's general condition was poor, and, therefore, the cortisone therapy was discontinued.

Case 4 was a case of pemphigus erythematosus with gradual control of the lesions by the administration of cortisone by mouth.

Case 5 was also a case of pemphigus erythematosus in which there was treatment with cortisone by mouth. The patient made an almost complete objective recovery.

Case 6 was a case of pemphigus vulgaris in which the lesions cleared after treatment with cortisone by mouth and heparin sodium (Depo-Heparin).

Case 7 was an extremely severe case of pemphigus vulgaris in which the lesions cleared on two occasions while the patient was receiving cortisone by mouth.

Case 8 was a case of pemphigus vulgaris in which the skin cleared with oral cortisone therapy, only to become worse, and the patient ultimately died despite resumption of the administration of cortisone by mouth.

COMMENT

The relative scarcity of patients with pemphigus precluded the use of control patients treated with blank tablets, but our experience and that of many others have proved that the eruptive and general phenomena of pemphigus can be controlled in many patients with parenteral use of cortisone.

The laboratory reports indicate that the responses to oral use of cortisone are about the same as the responses to the drug when used parenterally.

In our experience the clinical response to oral therapy closely paralleled the response to the parenteral use of the drug.

CONCLUSIONS

1. Oral administration of cortisone is clinically as effective in the treatment of pemphigus as is the use of the drug parenterally.

2. We have the impression that somewhat larger oral doses are necessary for the control of the disease.

3. The laboratory responses to oral administration closely parallel the responses to its parenteral use.

4. With careful observation toxic phenomena can be controlled.

5. The ease of administration makes oral administration of cortisone the treatment of choice for pemphigus.

6. Cortisone does not cure pemphigus. It merely controls the symptoms of the disease, and, as in arthritis, the patient must be followed indefinitely and supportive treatment with the drug given.

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SODIUM SULFACETAMIDE IN TOPICAL THERAPY

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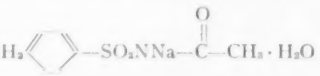
KATIOFSKY [1] in 1939 reported his experience with a new sulfonamide, sodium sulfacetamide, in the treatment of diseases of the eye. His article initiated a series of studies of the drug in the management of trachoma, ophthalmia neonatorum, and other morbid conditions of the ocular tissues. The early reports all appeared in the German literature, but in 1941 Robson and Scott [2] in England used the drug in the local treatment of experimental pyocyaneus ulcers of the cornea, and later Robson and Tebrich [3] reported on the penetration of the drug into the eyes of rabbits. The first mention of the drug in the American literature was by Strakosch and Clark [4] in 1943 in a comparative study on the penetration of sulfonamides into the skin. Sodium sulfacetamide, or Sodium Sulamyd [5] (Schering),* is the monohydrated sodium salt of N-sulfanilylacetamide. It is highly soluble at the physiologic pH of 7.4, and the structural formula may be represented as follows:



My attention was first directed to this drug by an ophthalmologist who recommended its use for a severe conjunctivitis and blepharitis complicating an impetigenized seborrheic dermatitis. The details of this case were as follows:

E. J. B., aged 46, was first seen in November, 1950, with the history of a persistent itching and scaling eruption of the scalp of 10 years' duration. Various proprietary and prescribed preparations had controlled but never eradicated the eruption. Two weeks prior to his first visit the eruption extended to involve the face, neck, midback, midchest, and pubic area. In the past week the arms had become involved, and serous oozing and crusting supervened.

Physical examination revealed a well-developed man with an eruption of the scalp, face, neck, upper back, midchest, upper arms, and pubic area. In the scalp it appeared as follicular papules covered with a yellowish scale, with confluence, serous exudation, and crusting extending from the occiput to the upper back. Over the midchest, flexure of the left elbow, and pubic area the eruption was confluent and eczematized. There were a severe blepharitis and purulent conjunctivitis.

A consulting ophthalmologist advised the instillation of 10% sodium sulfacetamide ointment into the conjunctival sac and to the lids three times daily. When the patient was seen one week later, the conjunctivitis and blepharitis had cleared, and the serous oozing and crusting in the other areas involved had been controlled. The patient then admitted that since he had experienced such immediate and gratifying results with the ointment which he was using in his eyes, he had

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* Material and technical assistance for this study were furnished by the Division of Clinical Research, Schering Corporation.

discontinued the treatment as outlined for him and on his own initiative extended its use to all of the other areas involved. Under its continued use he made favorable progress and was able to return to work in three weeks.

Encouraged by this gratifying result with the use of a drug which apparently had been overlooked in dermatologic therapy, or crowded out by the growing family of antibiotics, we directed studies toward determining its antibacterial activity, penetration into the skin, and clinical effectiveness in seborrheic dermatitis as well as in some cases of primary bacterial cutaneous infections.

GROWTH AFTER INCUBATION AT INDICATED PERCENTAGE OF SODIUM SULFACETAMIDE (AGAR PLATE METHOD)

ORGANISM	5%	3%	2%	1%	0.8%	0.6%	0.4%	Control	
Streptococcus Group C	–	–	±	±	±	±	++	+++	Gram +
Streptococcus faecalis	–	–	±	±	±	++	+++	+++	
Staphylococcus albus	–	±	±	++	++	++	++	+++	
Staphylococcus aureus	–	±	++	++	++	++	+++	+++	
Corynebacterium simplex	–	–	–	–	–	–	++	+++	
Bacillus subtilis	–	–	–	–	–	–	–	+++	
Neisseria flava	–	–	–	–	–	–	–	+++	Gram –
Escherichia coli	–	–	–	–	–	–	±	+++	
Pseudomonas pyocyanea	–	–	–	–	–	–	–	+++	
Klebsiella pneumoniae	–	—	–	–	–	–	–	+++	
Aerobacter aerogenes	–	–	–	–	–	–	++	+++	
Proteus vulgaris	–	–	–	±	++	++	++	+++	

Table 1

ANTIBACTERIAL ACTIVITY

Using the agar plate method and concentrations of sodium sulfacetamide varying from 0.4% to 5%, we found that growth was inhibited in all but two instances with a concentration of 3% and in all instances with a 5% concentration (Table 1). The organisms used included those commonly isolated from cutaneous pyogenic infections and others to make an equal number of Gram-positive and Gram-negative organisms. It should be emphasized that, although only one strain of bacterial organism may be isolated from a site of infection, in the majority of cases two or more different organisms are isolated. The value of a drug effective against both Gram-positive and Gram-negative organisms is obvious. The opinion is also held by some [6] that the Gram-negative bacilli, particularly Proteus and Pseudomonas, are increasing in incidence and importance in cutaneous pyogenic infections. Both of these organisms are inhibited by sodium sulfacetamide.

Since their introduction the antibiotics have played an increasingly important role in the management of cutaneous bacterial infections. However, some of them

have shortcomings, such as a limited spectrum of effectiveness, allergenic potential, instability, toxicity, or the development of cutaneous moniliasis. A comparison of the in vitro antibacterial activity of sodium sulfacetamide and four commonly used antibiotics, employing the same organisms as those used in the sensitivity tests, reveals an important phase in the shortcomings of the antibiotics, namely the limited spectrum of effectiveness, as shown in the accompanying chart. It would require a combination of bacitracin and neomycin, together with polymyxin B to control the Pseudomonas, to equal the effective range of sodium sulfacetamide.

COMPARISON OF IN VITRO ANTIBACTERIAL ACTIVITY OF SODIUM SULFACETAMIDE AND ANTIBIOTICS

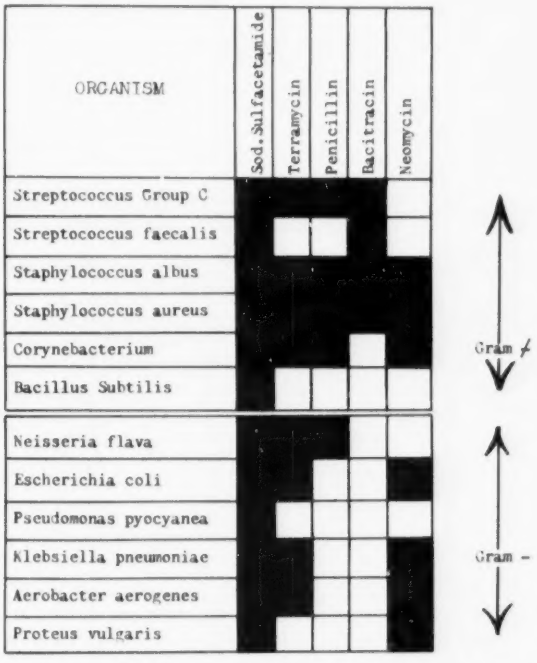

Chart assembled from data published by manufacturers of antibiotics and unpublished data from Division of Clinical Research, Schering Corporation.

PENETRATION

Sodium sulfacetamide is highly soluble at the physiologic pH of 7.4, a fact directly related to penetration and absorption. Maximum absorption and minimum irritation are achieved with solutions of a hydrogen ion concentration approaching neutrality. Of four tested sulfonamides, Toland and Kornblueh [7] found that in pH value sodium sulfacetamide solution responds most nearly to this requirement (Tables 2 and 3). A 20% concentration of sodium sulfacetamide in plasma of pH 7.05 being used, the pH was recorded at 7.68, while that for the other sulfonamides ranged considerably higher. These figures show clearly that sodium sulfacetamide gives in vitro, in comparison with three other sodium salts of sulfonamide derivatives, not only the highest concentration but also the lowest pH, approaching the

normal pH of blood. In studies of penetration into the skin, Strakosch and Clark [4] found that sodium sulfacetamide gave greater penetration than either sulfathiazole or sulfadiazine, especially in the injured or abraded skin. It was also their observation that the type of ointment base used, whether of the oil-in-water or water-in-oil variety had very little or no effect. Leopold and Steele,[5] however, found that the oil-in-water type base allowed greater penetration in an inflamed or denuded cornea.

CLINICAL OBSERVATIONS

This study is based on 100 unselected cases, 76 cases of seborrheic dermatitis (Table 4) and 24 cases of other dermatoses (Table 5), including both primary and secondary cutaneous bacterial infections. The age of the patients ranged from 4

COMPARISON OF FOUR SULFONAMIDES IN SATURATED AQUEOUS SOLUTION

	Conc.	pH
Sodium Sulfacetamide	56.9%	9.24
Sodium Sulfadiazine	51.7%	9.88
Sodium Sulfathiazole	28.6%	10.42
Sodium Sulfapyridine	50.0%	10.78

Table 2 (from Toland and Kornbleuh)

THE pH READINGS OF SODIUM SALTS IN PLASMA OF pH 7.05 IN A CONCENTRATION OF 20%

	pH
Sodium Sulfacetamide	7.68
Sodium Sulfadiazine	9.00
Sodium Sulfathiazole	9.28
Sodium Sulfapyridine	10.48

Table 3 (from Toland and Kornbleuh)

months to 76 years, and there were about as many males as females. The cases of seborrheic dermatitis were classified on the basis of extent and degree as follows:

1. Severe: Cases with involvement of the entire scalp and extension to the face, neck, and glabrous skin and/or eczematization, oozing, and crusting
2. Moderate: Cases with involvement of the scalp, eyebrows, and nasolabial angles
3. Mild: Cases with diffuse or patchy involvement of the scalp only

In all cases except those classified as mild, both an ointment and a shampoo containing sodium sulfacetamide were used. Twelve cases in the latter group obtained both subjective and objective improvement with weekly use of the shampoo only. The ointment consisted of a 10% strength in an oil-in-water type base. The shampoo contained 3% sodium sulfacetamide in an aqueous combination of protein derivatives and fatty acid radicals of high molecular weight, classified as a soapless detergent and marketed under the trade name Dara. This shampoo was chosen because of its compatibility with the drug and patient acceptability due to its foaming properties with hard water. The ointment was used once or twice daily according to the severity of involvement, and the shampoo, twice weekly till the subjective

symptoms were controlled and then once weekly. No special instructions were given in regard to shampooing except to advise that the head should be wet thoroughly with warm water and the shampoo worked into the scalp until lather was obtained, followed by rinsing and repetition of the process.

SUMMARY OF RESULTS OBTAINED IN THE THERAPY OF SEBORRHEIC DERMATITIS WITH SODIUM SULFACETAMIDE OINTMENT AND SHAMPOO

Classification of cases	Number of cases	Complete control	Improved	Unimproved
Severe	21	9	7	5
Moderate	30	17	13	0
Mild	25	20	5	0
Totals	76	46	25	5

Table 4

SUMMARY OF RESULTS OBTAINED IN THE THERAPY OF OTHER DERMATOSES WITH SODIUM SULFACETAMIDE OINTMENT

Diagnosis	Number of Cases	Complete Control	Improved	Unimproved
Alopecia Areata	1			1
Contact Dermatitis	1			1
Folliculitis	2	2		
Impetigenized Dermatitis	4	4		
Neurodermatitis	1			1
Neurotic Excoriations	2	2		
Otitis Externa	5	4	1	
Psoriasis	3			3
Sycosis Vulgaris	5	5		
Totals	24	17	1	6

Table 5

A series of patch tests was performed on 50 persons with the shampoo, ointment, and a 30% solution. These were read in 24 and 48 hours. After a two-week interval the tests were repeated on the same area of the skin of the same subjects. No evidence of irritation or sensitization was detected. However, among the cases treated, four instances of reactions were encountered. One followed application of a 30% solution to a contact dermatitis of the eyelids, and one followed application of the same solution to the eyes and lids in a case of neurodermatitis. One followed

the application of the ointment and another use of the shampoo in cases of seborrheic dermatitis. These reactions account for two cases listed as unimproved in the series of cases of seborrheic dermatitis and two cases listed as unimproved in the series of other dermatoses treated.

OBSERVATIONS AND RESULTS

During the period of treatment and observation, which ranged from one to six months, no other therapy was employed. In the event that such therapy was deemed necessary because of extension of the eruption or irritation, the case was recorded as unimproved. Observations were made weekly for four weeks and then biweekly, each case being interpreted according to the following criteria:

1. Complete control: Absence of subjective symptoms and all objective signs of disease
2. Improved: Absence of subjective symptoms but persistence of objective signs of active disease
3. Unimproved: Extension or aggravation of the disease process

On this basis, of the 76 cases of seborrheic dermatitis with varying severity of involvement, 46 were completely controlled, 25 were improved, and 5 were unimproved. Since practically all these patients had used various shampoos, lotions, and medicaments prior to the study, a separate control group was not set up. Naturally, the best results were obtained in the group with mild involvement, almost half of whom achieved results by use of the shampoo alone. In these cases both signs and symptoms were controlled in two to four weeks.

The smallest number of cases of complete control were found among the severe cases. In this group there were two instances of unfavorable reaction, one to the shampoo and one to the ointment, raising the total of unimproved cases to five. However, there was striking improvement in the cases complicated by secondary bacterial infection, serous oozing, and crusting.

In the group of 24 patients presenting other dermatoses, 17 were completely controlled, 1 improved, and 6 unimproved. The ointment alone was used in conditions involving the glabrous skin alone, while both the ointment and the shampoo were used in the cases of psoriasis and alopecia areata. Although the number of failures in this small group was relatively high, it is noteworthy that complete control was achieved in all the primary bacterial cutaneous infections except in one case of otitis externa, which showed definite improvement.

SUMMARY

The chemotherapeutic effectiveness of sodium sulfacetamide was studied in the management of 100 patients, 76 with seborrheic dermatitis of varying extent and severity and 24 with other dermatoses, including primary bacterial cutaneous infections.

This drug exhibits an in vitro antibacterial activity against a majority of the organisms most commonly found in cutaneous pyogenic infections. It is effective in low concentrations against both Gram-positive and Gram-negative organisms, and its spectrum compares favorably with that of a combination of bacitracin and neomycin against the organisms tested. This fact suggests its possible usefulness in substitution therapy in cases in which the organism is resistant to the antibiotic or the patient has become sensitized to the antibiotic.

The high solubility of sodium sulfacetamide at the physiologic pH of 7.4 is the basis for its high degree of penetration and absorption in comparison with other sulfonamides. Although it seems to be equally effective in an oil-in-water or a water-in-oil type emulsion base, there is some evidence that the former allows greater penetration in the inflamed or abraded skin.

Repeated patch tests with the preparations used revealed no evidence of irritation or sensitization. However, during the course of the study four instances of irritation were encountered. Two patients reacted to a 30% solution instilled into the eyes, one to the shampoo and one to the ointment.

Of the 76 cases of seborrheic dermatitis with varying degrees of severity of involvement, 46 were completely controlled in from two weeks to six months. Twelve patients used only a shampoo containing 3% sodium sulfacetamide, while the remainder used a 10% sodium sulfacetamide ointment for varying lengths of time, finally completing their treatment with the shampoo alone. Improvement was striking in cases complicated by secondary bacterial infection, oozing, and crusting.

Of the 24 cases comprising other dermatoses, including primary bacterial cutaneous infections, complete control was achieved with the use of 10% sodium sulfacetamide ointment in 17. The drug exerted no influence in one case each of alopecia areata, contact dermatitis, and neurodermatitis and in three cases of psoriasis. The effectiveness of the drug in all types of primary bacterial cutaneous infection was noteworthy.

1115 Empire Building (22).

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ABSTRACT OF DISCUSSION

Dr. Stanley Crawford, Pittsburgh: Dr. Duemling is to be commended for his courage in reviving the use of sodium sulfacetamide and demonstrating its value as a topical agent in the treatment of pyococcic and seborrheic dermatoses. Several years ago the use of all sulfonamide derivatives in the local management of cutaneous infections was rightly condemned because of their high sensitizing rate and the subsequent danger from their use in more serious conditions. Sodium sulfacetamide, or sulfacetimide, as it is sometimes spelled, the nitrogen group involved making no practical difference, was employed 15 years ago by European ophthalmologists as a topical antibacterial agent in inflammatory conditions of the eye. Today many ophthalmologists consider it superior to silver nitrite in preventing gonorrheal ophthalmia of the newborn and an effective bacteriostatic remedy in conjunctivitis and corneal injuries. A few have experienced irritation from its use in the eye. Sodium sulfacetamide was also used in Europe for a brief

period as an effective antibacterial remedy in pyogenic infections of the skin, and no cases of sensitivity to the drug developed, but its use was discontinued without apparent reason and then forgotten by dermatologists. Later came the ban on all sulfonamide derivatives in dermatological therapy, and sodium sulfacetamide receded into limbo.

The modern sulfonamide drugs act systemically in acid or alkaline media with an absence of crystalluria, and because of their low incidence of adverse reaction and sensitization they are often used effectively by urologists in renal infections. Sodium sulfacetamide, like the newer sulfonamides, when administered orally acts systemically in acid or alkaline media without producing crystalluria. It has a high index of bacteriostatic effectiveness against Gram-positive and Gram-negative micro-organisms and a very low sensitizing rate and may be considered a safe drug for topical therapy.

Allergic reactions following its use locally on the skin are extremely rare and are practically negligible when they occur. Every therapeutic agent is capable of inducing sensitivity in a certain number of patients. Evidently sodium sulfacetamide is a nonirritating, nonsensitizing, and effective bacteriostatic drug when used topically on the skin in the treatment of primary and secondarily infected pyogenic lesions due principally to staphylococcic or streptococcic micro-organisms or both.

Many of the modern antibiotic agents in ointment form have been disappointing in the treatment of this class of dermatoses. Dr. Duemling's favorable experience with sodium sulfacetamide in the treatment of cutaneous infections may make its use in ointment form a welcome addition to the antibacterial remedies now available for topical use on the skin. Our brief experience with it in ointments of 5 or 10% strengths in the treatment of impetiginous dermatoses has been satisfactory. His successful results with sodium sulfacetamide in the treatment of seborrheic dermatitis are encouraging, and using it incorporated in a soapless fatty acid liquid detergent as a shampoo for seborrheic conditions of the scalp is an innovation. If his gratifying results are repeated by others, then the field of dermatological therapy has been rendered a service.

Dr. W. W. Duemling, San Diego, Calif.: I should like to thank Dr. Crawford for his discussion and his report on the use of sodium sulfacetamide. This drug is widely used by ophthalmologists, and, although occasional reactions have been reported, they have not been of sufficient number or severity to preclude its use. It is readily available on the market and in the amounts indicated can be compounded into an ointment or shampoo at a nominal cost.

CHROMOBLASTOMYCOSIS

Report of Nine Cases from a Single Area in Louisiana

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CHROMOBLASTOMYCOSIS is ordinarily regarded as an uncommon type of fungous infection anywhere in the world and as an actually rare infection in the United States. When Carrión [1] published his article on the subject in 1950, he included a critical analysis of all the cases reported up to 1947, of which he accepted 157 as verified. Of these, 43 had occurred in Cuba, 41 in Brazil, 15 in Puerto Rico, 12 in South Africa, and 9 in the United States. The remaining cases occurred in small numbers in various parts of the world with the exception of Asia. The apparent immunity of that continent now no longer exists, a case of the disease having been reported from China in 1951.[2]

The first case of chromoblastomycosis in the United States occurred in Massachusetts in 1915 and was described by Medlar [3] and Lane [4] in separate publications. Since Carrión's [1] review of the literature, three other cases have been reported in this country, by Mundt and Moore [5] in Louisiana, by Conway and Berkeley [6] in New York, and by French and Russell [7] in Michigan (their patient apparently having contracted his disease in South Carolina). Moore, Cooper, and Weiss [8] reported two cases from Missouri in 1943, but with this exception, all observers and groups of observers have reported only single cases, though Moore [9] had collaborated in an earlier report, also from Missouri, in 1940.

The purpose of this communication is to put on record nine cases of chromoblastomycosis observed in the New Orleans area in the last two years by a single group of observers. Seven patients were seen in the Dermatology Clinic of Charity Hospital of Louisiana at New Orleans and the other two in private practice in the city. These 9 cases raise the number reported in the United States to 21 and the number reported from Louisiana to 10. The significant feature of this enumeration is obvious, that 9 of these 21 cases were observed in the same area by a single group of observers over

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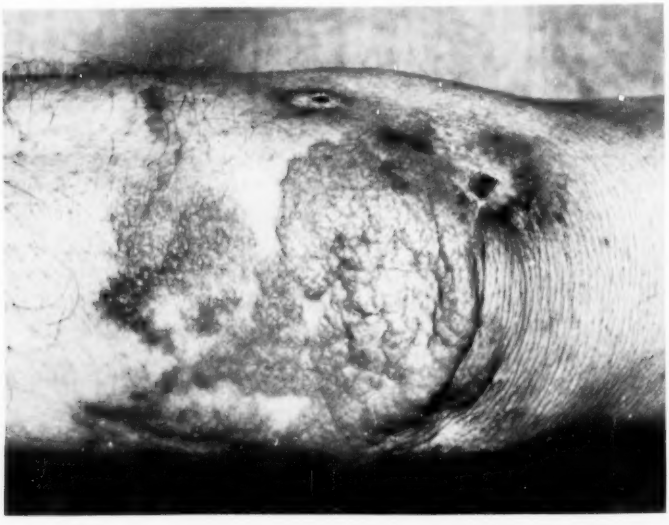
a 2-year period, in contrast to 12 cases observed in the entire country during the preceding 38 years. The implications are twofold: 1. This lesion is apparently not as uncommon as it has heretofore been supposed to be. 2. Cases will continue to be overlooked unless the disease is borne in mind and is given careful consideration in the differential diagnosis of all granulomatous lesions of the skin.

METHODS OF STUDY

All nine of these patients presented chronic granulomatous lesions of the skin. Scrapings from the advancing edges of the lesions were therefore investigated in the laboratory of the Department of Microbiology, Louisiana State University School of Medicine, by the following methods:



Chromoblastomycosis of left elbow of two years' duration.

1. Fresh wet preparations in 20% potassium hydroxide were examined microscopically for fungi. If typical dark-brown, oval, septate bodies 6 to 12 μ in diameter were found, a tentative diagnosis of chromoblastomycosis was made.

2. Scrapings were inoculated on Sabouraud's glucose agar and were incubated at room temperature. The cultures were identified by microscopic study of the mycelial and spore morphology as either Hormodendrum pedrosoi, Hormodendrum compactum, or Phialophora verrucosa.

3. Scrapings were suspended in isotonic sodium chloride solution containing 50 units of penicillin and 100 γ of streptomycin per cubic centimeter. The treated solution was injected into the yolk sacs of 6 to 8 day embryonated eggs according to the method described by Brueck and Buddingh.[10] If numerous typical dark-brown, oval, septate bodies could be identified four to six days later in yolk sac preparations in 20% potassium hydroxide, the tentative diagnosis of chromoblastomycosis was regarded as confirmed.

4. A biopsy specimen was examined for the presence of typical septate bodies and the characteristic histopathologic reaction.[1]

ANALYSIS OF CASES

The essential data in these nine cases of chromoblastomycosis are presented in tabular form and require little additional comment. Six patients were white and three Negro. Seven were men and two women. All were adults, ranging in age from 34 to 79 years. The figures are far too small to permit conclusions, but it might be pointed out that most patients in this series were considerably more advanced in years than those in Carrión's [1] world-wide collection of cases. In that group, the ages of 77 of the 109 patients were stated to be between 20 and 50 years. In the New Orleans series, only one patient was under 40 years of age, and six were 54 years of age or older.

The occupations of all these patients, or their environments, were such that they were brought into contact with the soil and with wood, on which the fungi responsible for this disease are natural saprophytes. This observation is in accord with most other reports, in which the same contacts were noted. French and Russell's [7] patient actually had a sliver of wood at the site of the lesion in the dorsum of the wrist, though the lesion, unfortunately, was excised before they saw him and no cultures were made. In Gomes' [11] case the fungus isolated from the lesion on the hand (Hormodendrum) was also isolated from the eucalyptus tree from which the man received his original wound. The chronicity of the disease is always evident from the duration. In the New Orleans series it ranged from 6 months to 20 years. In eight cases the duration was two years or more, and in six it was three years or more.

In each instance the lesions developed on exposed areas of the skin. The forearm or elbow was affected in four cases, the dorsum of the hand in three, and the foot or leg in two. This distribution is not in accord with Carrión's [1] conclusion, based on his analysis of the world-wide series, that the lesion appears predominantly on the lower extremities. It will be remembered that in the first case reported in the United States * the lesion was on the buttock.

Six of the lesions were plaque-like and crusted, as in the accompanying illustration. Two were nodular and surrounded by scar tissue. One was granulomatous. Whenever sinuses were present or exudate could be expressed from beneath crusting lesions, the discharge was a milky-white fluid. Some of the lesions were extensive. One, in which the duration was 20 years (Case 5), involved the anterior and lateral aspects of the foot and leg to just below the knee. Two others, both on the elbow, were, respectively, 6 by 3 in. (15.2 by 7.6 cm.) (Case 4) and 8 by 1½ in. (20.3 by 3.8 cm.) (Case 9).

The etiologic diagnosis was established in seven cases by microscopic demonstration of the typical dark-brown, oval, septate bodies in potassium hydroxide preparations. Cultures on Sabouraud's medium and inoculations of chick embryo yolk sacs were positive in eight cases. Biopsy specimens were positive in seven of the nine cases. In one instance (Case 1), in which both culture and wet preparation were negative, biopsy provided the only means of diagnosis.

Two patients in this series, a 43-year-old Negro man (Case 5) and a 79-year-old white man (Case 7), refused treatment and left the hospital against advice. Two patients were treated by x-rays too recently to permit any conclusions as to results. Three patients were treated by potassium iodide. In one instance (Case 1) no results

*References 3 and 4.

Summarized Data in Nine Cases of Chromoblastomycosis Observed in Louisiana

Case No.	Source	Race	Sex	Age	Occupation	History	Lesion	Diagnosis	Fungus *	Therapy, Results
1	Charity Hospital	N	M	34	Unloading oyster shells; working on country roads	Duration 5 yr.; began as small boil, which repeatedly broke down, drained, and healed partially, but never completely, by scarring; local injuries reactivated lesion	Lateral aspect, middle third, right arm; scar 1½ in. (3.8 cm.) in diameter, round, depigmented, atrophic; attached inferiorly to scar was 1½-in. round, elevated, plaque-like, verrucous, scaly lesion	Biopsy positive; culture and wet preparation negative	.....	Potassium iodide in increasing doses; no results evident; patient refused to continue treatment
2	Charity Hospital	N	M	64	Farmer; much contact with wood	Duration 6-8 mo.; patient referred by local physician for diagnosis and treatment of chronic granuloma	Dorsum left hand; round, elevated, crusted lesion 1½ in. in diameter, with 5 bluish papules extending upward from its surface; unroofing lesion revealed sinus from which thin, milky secretion exuded	Biopsy, wet preparation, culture positive	H. pedrosoi	Excision, skin graft; cure
3	Charity Hospital	W	M	67	Fishing, hunting	Duration 2 yr.; began as slowly enlarging lump, which broke down and drained at intervals and gradually assumed warty characteristics; diagnosed as psoriasis by several physicians	Dorsum left hand; large, red, verrucous lesion 2 by 3 in. (5 by 7.6 cm.), slightly elevated above surface, firm, nontender; in margin were several crust-covered sinuses from which thin, milky fluid could be expressed	Biopsy, wet preparation, culture positive	P. verrucosa	X-ray, potassium iodide; no evident results, but when patient returned 2 yr. later, lesion was completely healed and only 3 in. depigmented scar was present; result not regarded as related to therapy
4	Charity Hospital	W	M	62	Carpenter	Duration 2 yr.; began as pimple, gradually increasing in size	Left elbow; scaly, erythematous, elevated, plaque-like lesion, 6 by 3 in. (15.2 by 7.6 cm.)	Biopsy, wet preparation, culture positive	H. pedrosoi	Potassium iodide, iontophoresis with copper sulfate both ineffective; surgery refused
5	Charity Hospital	N	M	43	House wrecker, odd jobs	Duration 20 yr.; began as sore which extended rapidly; constant drainage from many areas; patient also had pulmonary tuberculosis	Anterior and lateral aspects of left foot and leg to just below knee; multiple papules 1 to 1½ in. (2.5 to 3.8 cm.) in diameter, with verrucous surfaces, set in heavily scarred tissue; many draining sinuses which excreted thin, milky fluid	Biopsy, wet preparation, culture positive	H. pedrosoi	Therapy refused
6	Charity Hospital	W	F	54	Housewife, lives in country	Duration 6 yr.; draining ulcer which broke down, healed, and broke down again; increase in size	Lateral aspect right leg; raised, nodular, verrucous lesion 2 in. in diameter; shallow ulcer revealed when crust removed	Biopsy, wet preparation, culture positive	H. pedrosoi	X-ray ineffective; surgical excision, skin graft, twice; cure
7	Charity Hospital	W	M	79	On relief, lives in country	Duration 3 yr.; began with bruise, followed by sore; similar lesion lateral to original	Left elbow, medial and lateral aspects; rough, verrucous, papular lesions set in large, flat scar covering entire elbow; medial lesion 4 by 1 in. (10.1 by 2.5 cm.); lateral, 1½ in. in diameter	Biopsy, wet preparation, culture positive	H. pedrosoi	Refused treatment
8	Private patient	W	M	73	Wood worker	Duration 3 yr.; began as pimple, from which pus exuded on pressure; slow increase in size; previous treatment instituted without smears or cultures	Dorsum right hand; rough, verrucous, papular lesion, 1 in. in diameter, with 2 small draining sinuses from which thin, milky pus could be expressed	Biopsy negative; wet preparation and culture positive	H. pedrosoi	X-ray; too soon to determine results
9	Private patient	W	F	48	Housewife, lives in country	Duration 3 yr.; began as wart-like sores which repeatedly broke down, drained, and healed by scar tissue	Medial aspect right forearm; lesion 8 by 1½ in. (20.3 by 3.8 cm.) consisted of 8 nodular, verrucous lesions, ½ to 1 in. (1.3 to 2.5 cm.), in scar tissue; 2 lesions drained thick, milky pus	Biopsy negative; wet preparation and culture positive	H. pedrosoi	X-ray; too soon to determine results

* Designation by cultural characteristics.

were evident in spite of increasingly large dosages, and the man declined further treatment. In one case (Case 4) iontophoresis with copper sulfate was also employed. There was no improvement in the lesion, and surgery was declined. In the third case (Case 3) x-ray therapy was also used. No immediate results were apparent, and treatment was discontinued. The patient returned two years later with no evidence of the lesion other than a 3 in. (7.6 cm.) depigmented scar. The good results were not attributed to the therapy employed. Two patients were cured by excision of the lesion followed by skin graft. One (Case 6) had previously been treated by x-rays, without evident improvement. The first graft did not take, but healing was excellent after the second was applied.

COMMENT

Since chromoblastomycosis was first described by Pedroso of São Paulo, Brazil, in 1911, it has been extensively studied by a number of other observers. Conant and Martin's [12] review of the subject in 1937 and Carrión's [1] study in 1950 cover all phases of the pathogenesis, pathologic process, and immunologic considerations and also describe in detail the morphologic and cultural characteristics by which the causative agents may be identified.

It is not our intention in this communication to present evidence which can be considered determinative for the taxonomy and nomenclature of the fungus responsible for this disease. The problems involved can be inferred from the several names currently given to it. Experience gained from our studies supports Carrión's [1] suggestion that the generic designation Fonsecaea pedrosoi should be used instead of Hormodendrum because it more accurately denotes the causative agent of chromoblastomycosis. This fact was particularly evident from the identical appearance of the septate bodies in the lesions of the disease and in the experimental infections produced in the yolk sacs of embryonated eggs. In this respect this genus is quite distinct from a species of Hormodendrum recently isolated in our laboratory from a fatal systemic infection and characterized by the extensive growth of mycelial elements in the affected tissues. It is readily established in the yolk sac of embryonated eggs, in which it grows as an extensive mass of mycelial elements. These distinctive behavior patterns clearly distinguish the genus Fonsecaea from Hormodendrum.

The nine cases of chromoblastomycosis reported in this communication were identified as the direct result of the attention recently devoted in our departments to all varieties of mycotic infections and the provision of facilities for the proper examination of material obtained from the lesions, including facilities for the definitive identification of fungi by cultural methods. As already noted, these 9 cases were collected in this single area in a 2-year period, while only 12 cases had been reported in the entire United States during the preceding 38 years. These cases did not differ in any important respect from the cases reported from other parts of the country, and the chief lesson of the experience is simply that if presumably rare diseases are looked for with sufficient care and attention, they will frequently prove to be a great deal commoner than they are ordinarily supposed to be.

The small number of reported cases of chromoblastomycosis, and the wide variety of treatments employed in them, make it impossible to draw conclusions as to the value of any single therapeutic method. Of all the chemotherapeutic agents employed, according to Carrión,[1] only the iodides seem to have been effective, though careful

follow-up observations do not furnish convincing evidence of their value. They were not useful in our own series. Carrión's comment on x-ray therapy duplicates his remarks on iodides. Our own experience is still inconclusive. Surgical excision seems to have produced the best results, but it has its limitations in extensive lesions. In Conway and Berkeley's[6] case a cross leg pedicled flap was required to cover the large defect left after removal of the lesion, together with exposure of the tendons of the peroneus longus and peroneus brevis muscles and partial removal of the cruciate crural ligament and extensor digitorum brevis muscle. Carrión believes that under some circumstances amputation may best solve the therapeutic problem. It would have been far too radical a procedure to consider in any case in our series.

SUMMARY

Although chromoblastomycosis is ordinarily described as a rare lesion in the United States, in which only 12 cases were reported in the last 38 years, 9 cases have been recognized in southern Louisiana in the last two years.

In seven cases the diagnosis was established by positive biopsy and by the demonstration of the typical brown, oval, septate bodies of the causative fungus in fresh wet potassium hydroxide preparations of scrapings from the lesions. Cultural methods were also employed. In two cases wet preparations and cultures were positive and biopsy negative. In the remaining case only biopsy was positive.

The point to be emphasized in this report is the importance of considering chromoblastomycosis in the diagnosis of all chronic verrucous or granulomatous lesions of the skin in Louisiana.

The materials for this paper were being assembled by Dr. James K. Howles, Professor of Dermatology and Syphilology in the Louisiana State University School of Medicine, at the time of his death, in April, 1953. His colleagues have considered it a privilege to complete the report of these cases.

ABSTRACT OF DISCUSSION

Dr. A. L. Carrión, San Juan, P. R.: It has been a pleasure to hear this report. The widespread geographic distribution of chromoblastomycosis; the severity of its symptoms, often leading to incapacity for work; the confusing variety of fungus species associated with the infection, and the lack of an effective therapeutic agent to combat it have given that disease a prominent place among the major problems of human mycopathology.

The rate at which new cases of chromoblastomycosis have appeared in the past has been, indeed, comparatively low. It is generally believed, however, that the incidence of infection will be found to be much higher when physicians become better acquainted with the disease and are led to bear it in mind in the differential diagnosis of granulomatous skin lesions. The presenters have laid due emphasis on this point and have offered strong evidence to support it by placing on record nine cases of chromoblastomycosis discovered within a comparatively small area over a period of two years by a single group of workers. This is, indeed, a startling observation.

There is no doubt in my mind that the established incidence of a disease in a given region may represent, to a certain extent, the interest of local physicians on that disease. However, I venture to speculate on the possible existence of other conditions favorable to infection which would lead to the concentration of cases in certain regions.

The discovery of a concentrated focus of chromoblastomycosis in southern Louisiana is most important, not only from the viewpoint of epidemiolgy, but because it offers a unique opportunity to conduct field studies on prevailing conditions in an area where the infecting fungi would seem to be present in ponderable quantities.

The observations of Howles and his associates obviously open two avenues of investigation: (1) a search into the mycologic flora of the soil in that part of the country with a view toward determining the natural habitat of the fungi causing chromoblastomycosis; (2) a search for the natural conditions that favor the development of these fungi.

One of the species causing infection, namely Phialophora verrucosa, has already been found in wood pulp used in the paper industry in Canada, and there is some evidence of the existence of the parasite in other wood material. But with regard to Fonsecaca pedrosoi, which is the commonest etiologic agent of the disease, there is no official report as yet on its isolation from nature, although a great deal of evidence points to the soil as its most probable habitat. Indeed, the majority of the patients are farmers who work without shoes and contract the initial lesion in some part of the foot. We have wondered about the low proportion of foot infections reported in New Orleans. It is possible that farm laborers in that area habitually wear shoes while working, which would protect them against infection. Be that as it may, soil cultures should be carried out extensively over the southern Louisiana area, being concentrated on points where patients have contracted the disease. Samples of soil should be taken from the superficial layers of the ground, including manure and decaying vegetable matter, and this material should be inoculated into proper laboratory media. When positive cultures are obtained—and the chances of success are good if the technical operation is adequate—the local environment of such foci could be studied to determine the temperature, humidity, chemical composition of the soil, hydrogen ion concentration, type of vegetable matter present, and other conditions that might influence the growth of the fungi. Furthermore, efforts should be made to determine possible infection in plants as well as in the animal population of the region, including autopsies of the animals, with histopathologic and cultural studies. An investigative project of this type may be expected to render valuable information about the life history of the fungus, the epidemiology of the disease, and the conditions leading to infection, all of which might have practical application in the problem of prophylaxis.

I should like to call attention to the careful laboratory technique followed by the authors for diagnosis. Certain other diseases, such as leprosy, leishmaniasis, syphilis, mossy foot, and so-called recurrent tropical lymphangitis, for example, may produce a dermatological picture closely resembling chromoblastomycosis. It should be emphasized that diagnosis must be based not only on clinical observations but also on the presence of the etiologic fungus in the epidermal scrapings, in the histopathologic sections, or in culture. With patience and careful technique we have never failed to recover the parasite in any of the authentic cases that have come to our attention.

The report on differential morphology noted between F. pedrosoi and a pathogenic species of Hormodendrum as produced by the authors, experimentally, in the yolk sac of embryonated eggs is an interesting observation. Should this be further confirmed, it would be another clear-cut, distinguishing feature between these two generic groups of fungi.

May I extend to the presenters my warm congratulations for a most interesting, instructive, and carefully evaluated report.

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EFFECT OF TREATMENT IN LATE LATENT SYPHILIS

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THE EVALUATION of therapeutic results in late latent syphilis is a difficult problem. There are no symptoms or signs that can be influenced by treatment, and serologic reversal is an uncertain criterion of successful therapy. The effectiveness of different kinds of treatment must be judged solely by the comparative incidence of subsequent clinical manifestations of the disease. Proper evaluation of any type of therapy will thus require the prolonged observation of many patients, but because of the recent revolution in antisyphilitic therapy, with an almost total switch to penicillin, we cannot afford to wait very many years to discover whether the newer treatment methods are effective.

Today penicillin is universally used as the sole therapeutic agent in latent syphilis. Penicillin is effective in early manifest syphilis and in late benign tertiary and neurosyphilis and is therefore presumed to be useful in the intervening latent stage, but proof of this assumption is lacking. The effectiveness of metal chemotherapy has been established reasonably well, and the abandonment of it can be justified only if we can demonstrate that penicillin is as good as, or preferably better than, the metals.

Without any treatment most cases of latent syphilis do not progress, and evaluation of a new method must be entirely comparative. The effect of penicillin must therefore be judged against a background of knowledge of the incidence of progression in untreated patients and in those treated by the older methods.

It has been customary in the study of latent syphilis to require a minimum observation period of several years in each patient for reasons that are not altogether

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clear. Blum and Barnett [1] reported a study of latent syphilis in 1948, in which they found that treatment results could be changed radically by varying the minimum observation period. The reason for this appeared to be that uncooperative groups showed poorer results with the longer observation periods because the number of cases remaining under observation was small, and an occasional patient returning because of illness due to progression had a profound effect on the percentage incidence of treatment failure.

An example of this statistical fallacy, taken from the report of these authors, shows the percentage incidence of clinical progression with various minimum periods of observation in two groups of virtually untreated patients (Table 1). In one of these groups, treatment was purposefully withheld, and the patients were presumably normally cooperative. In the other group, every effort was made to administer therapy, and the failure to do so was due solely to lack of cooperation.

It is evident that the incidence of progression in the uncooperative group could be made to appear either more or less than that in the control group by changing the observation requirement, whereas actually there is no reason to suppose that there is any difference between the two groups.

TABLE 1.—*Effect of Different Minimum Periods of Observation on Apparent Incidence of Progression*

Minimum Observation Period, Yr.	Incidence of Progression, %	
	Untreated	Uncooperative
None (entire series)	2.5	1.4
1	3.9	4.1
3	4.8	8.1
5	5.3	10.9

Blum and Barnett concluded that the minimum observation period should be eliminated and that progressions should be expressed, not in relation to the number of individual patients, but to the total number of years of patient observation, or, in other words, to the years of known exposure to the risk of progression. This method provides a more random sample of cases for statistical analysis, and it also gives more weight to the cases which have been observed for a longer time. The total observation period is computed by simply adding the individual observation periods.

In the last three years, a cooperative study of late latent syphilis has been made in four San Francisco clinics: Stanford University, University of California, San Francisco City Clinic, and San Francisco Polyclinic. The purpose was not only to provide a better background of knowledge about the prognosis with and without treatment but, primarily, to collect preliminary data on the value of penicillin. Since one of the clinics (Stanford) was represented in both investigations, this new study is not entirely independent of that of Blum and Barnett.

A total of 2,470 patients were treated with metal chemotherapy and 231 with penicillin. Seventy-one percent of the patients were white, and 55% were male. In the penicillin-treated group a few patients also received some heavy metal in addition, but no patient was included who had been given more than 25 doses of arsenic or bismuth, or both. The penicillin dosage varied from 1,000,000 to 10,000,000 units, the commonest dose being 6,000,000 units. There were a very few lower

dosage schedules, and in most of these soluble penicillin was used in a dosage of 20,000 units every three hours for 60 doses. This made a total dosage of 1,200,000 units and was considered satisfactory treatment.

It is essential in any survey of the results of treatment in latent syphilis that each patient have a detailed physical examination, at least at the start and finish of the observation period. No case can be assumed not to have progressed just because the patient has been interviewed and appears in good health. Unfortunately, several thousand records were inadequate for this study because there was no terminal physical examination and therefore had to be discarded from the study.

Progressions were divided into four types: neurological, cardiovascular, benign tertiary (or gummatous), and possible. Since asymptomatic neurosyphilis was excluded as far as possible by pretreatment spinal fluid examinations, the instances of neurological progression were few, and they occurred only in those patients who developed clinical or serologic neurosyphilis after an initially negative cerebrospinal fluid examination. Cardiovascular progressions were limited to cases in which aortic regurgitation or aneurysm developed. Under the classification of possible progression were included patients who developed lesions that were not typically syphilitic but for whom that possibility could not be excluded. Such lesions included cerebrovascular accidents in hypertensive patients with negative cerebrospinal fluid, acute iritis, and other manifestations that might have been due to syphilis but were not established as syphilitic.

Treatment has been considered in two categories. Previous treatment is that given before the diagnosis of late latent syphilis was established in one of the cooperating clinics. The amount of such therapy has to be estimated from the history, and the estimate is often inaccurate. We divided the patients according to whether they had no treatment or very little treatment, i. e., 10 doses or less of arsenic or bismuth or both, before being seen in one of the cooperating clinics. According to subsequent treatment given in one of the four clinics the patients were divided into those who received fewer than 55 doses of arsenic or bismuth or both, and those who received more than 55 doses, or the equivalent of approximately one year of standard therapy. Most of the patients who were in the former group actually received much less than this maximum amount of 55 doses.

For three types of progression—cardiovascular, benign tertiary, and possible—the figures are remarkably consistent, as shown in Tables 2, 3, and 4.

The incidence of the three types of progression was greatly reduced in the group of patients who had received more than 55 doses of arsenic or bismuth or both, but only in those patients who had previously had a minimum amount of therapy. If previous treatment was reasonably adequate, subsequent therapy appears to have been of little additional benefit.

With neurological progressions, the picture is different. The incidence of such progression is negligible, as shown in Table 5, because all known cases of asymptomatic neurosyphilis were eliminated from the study. It was not possible to obtain pretreatment cerebrospinal fluid examinations in every patient, but each case demonstrating neurological progression must have had a negative cerebrospinal fluid examination before the progression.

The principal difference between the results shown in Table 5 and those in Tables 2, 3, and 4 is that in all four treatment categories of Table 5 the incidence of progression is almost identical. Since the late manifestations of neurosyphilis are

always preceded by asymptomatic neurosyphilis, these figures would suggest that treatment was not effective in this stage of the disease. The experience of most students of syphilis affirms, however, that treatment of asymptomatic (or latent) neurosyphilis is highly effective in preventing progression. We must conclude, therefore, that these few progressions have been included because of some fundamental error in the selection of cases. Probably occasional false negative cerebro-

TABLE 2.—*Incidence of Cardiovascular Progression per Century of Patient Observation in Relation to Treatment Received Before and After Diagnosis of Late Latent Syphilis*

	Subsequent Treatment, Doses	
Original Treatment	Less than 55	More than 55
Less than 10 doses of arsenic, bismuth, or both	0.62	0.15
More than 10 doses of arsenic, bismuth, or both	0.18	0.15

TABLE 3.—*Incidence of Benign Tertiary Progression per Century of Patient Observation*

	Subsequent Treatment, Doses	
Original Treatment	Less than 55	More than 55
Less than 10 doses of arsenic, bismuth, or both	0.40	0.06
More than 10 doses of arsenic, bismuth, or both	0.18	0.10

TABLE 4.—*Incidence of Probable Progression per Century of Patient Observation*

	Subsequent Treatment, Doses	
Original Treatment	Less than 55	More than 55
Less than 10 doses of arsenic, bismuth, or both	0.44	0.09
More than 10 doses of arsenic, bismuth, or both	0.11	0.05

TABLE 5.—*Incidence of Neurological Progression per Century of Patient Observation*

	Subsequent Treatment, Doses	
Original Treatment	Less than 55	More than 55
Less than 10 doses of arsenic, bismuth, or both	0.11	0.13
More than 10 doses of arsenic, bismuth, or both	0.11	0.15

spinal fluid reports led to erroneous diagnoses of latent syphilis in patients who actually had asymptomatic neurosyphilis at the start of therapy. Alternative explanations of this apparent paradox are that the number of neurological progressions was too small to permit of statistical comparison, or perhaps rare neurological progressions actually developed in patients with late latent syphilis who had been free of evidences of neurosyphilis at the time of their original examination.

All progressions, excluding the neurological ones, as shown in Table 6, display the same pattern as the separate tabulations of progressions, with considerable improvement from adequate treatment if there has been little therapy before but not much effect in patients who have already been reasonably well treated.

There seems to be but little question that metal chemotherapy did have a definite effect in decreasing the incidence of the progression in latent syphilis, and the hope

is that penicillin will do as well or perhaps even better. Unfortunately, our data on penicillin are still too limited to permit us to draw conclusions as to final outcome. However, certain trends can be detected which are of interest.

A comparison of our results with penicillin and with adequate metal chemotherapy is shown in Table 7. It is evident, since there have been two instances of

TABLE 6.—*Incidence of All Types of Progression Except Neurological per Century of Patient Observation*

Original Treatment	Subsequent Treatment, Doses	
	Less than 55	More than 55
Less than 10 doses of arsenic, bismuth, or both	1.46	0.30
More than 10 doses of arsenic, bismuth, or both	0.46	0.29

TABLE 7.—*Incidence of Progression After Metal Chemotherapy and After Penicillin Therapy*

Treatment	Cases	Progressions	Centuries of Observation	Progressions per Century
Arsenic and bismuth *	1,117	22	74	0.30
Penicillin	231	2	5.3	0.38

* More than 55 doses.

TABLE 8.—*Incidence of Progression in Relation to Wassermann-Fastness in Adequately Treated* Patients*

Serologic Results	Cases	Progressions	Incidence of Progression, %
Fast	450	19	4.2
Not fast †	439	6	1.4

* Penicillin or chemotherapy.
† Seronegative or only doubtfully positive one year after start of treatment.

TABLE 9.—*Incidence of Serofastness in Relation to Type of Treatment*

Treatment	Cases	Serofast		Seronegative at 1 Yr.	
		No.	%	No.	%
Arsenic and bismuth *	738	364	49	140	19
Penicillin	144	86	60	5	3.5

* More than 55 doses.

progression after penicillin therapy, that treatment with this drug does not guarantee arrest of the disease. In addition, we have seen two patients who developed cardiovascular syphilis, in one case aortic regurgitation and in the second aortic aneurysm, after treatment with penicillin. Both patients were treated for neurosyphilis and consequently could not be included in the present series of latent cases. One should not, of course, base any notion of incidence on only two instances of progression, but it is of interest that the frequency per century of observation happens to be practically the same after penicillin therapy and after adequate metal chemotherapy.

Aside from the prevention of progression, the only tangible evidence of therapeutic success is reversal of the serologic reaction. This has generally been considered to be unrelated to the outcome in late syphilis, but our results, as shown in Table 8, suggest that progressions may be more frequent in serofast cases.

Preliminary observations (Table 9) indicate that penicillin is probably less effective than metal chemotherapy in producing serological reversal. Tables 8 and 9, considered together, indicate that penicillin may not be as effective in late latent syphilis as the older therapy.

COMMENT

Antisyphilitic therapy in late latent syphilis appears to be effective in diminishing the incidence of subsequent clinical progression, even if it does not prevent progression entirely. However, if a patient has already received reasonably adequate therapy, retreatment is of little additional benefit.

The data on penicillin are too limited to justify any definite conclusions. Although penicillin appears to be effective, there is still enough uncertainty about its value that its use must be followed by prolonged and careful observation. There is absolutely no justification for administering penicillin to a patient with a positive Wassermann reaction and then dismissing him as cured. There is also no excuse for lowering our standards of diagnosis and giving penicillin to someone with doubtful serologic tests just to "play safe." If such a patient really has syphilis, the disease may well progress later, and the progression will be undiagnosed for some time because of overconfidence in the previous penicillin therapy.

SUMMARY

A series of 2,470 patients were treated for late latent syphilis with metal chemotherapy and 231 with penicillin.

The effectiveness of treatment was determined by the incidence of clinical progression per century of patient observation.

When arsenic or bismuth or both were used, the incidence of progression was less among patients who had received more than 55 doses than among patients who had received fewer doses, but only when previous therapy had been insignificant.

Penicillin did not completely prevent progression, but the data are too meager to allow satisfactory comparison with metal therapy. It appeared, however, that a higher incidence of persistently positive Wassermann reactions followed penicillin therapy than metal therapy.

Progressions were more frequent among Wassermann-fast cases than in those that were not Wassermann-fast.

ABSTRACT OF DISCUSSION

DR. HERMAN BEERMAN, Philadelphia: It requires careful and courageous workers to undertake a study of the effects of therapy on late latent syphilis, a phase of the disease in which the absence of definitive diagnostic criteria and accurate indices of benefit from treatment are bound to lead to frustration. Since Epstein and his co-workers were undaunted by these obstacles, their extensive studies of this problem have, so to speak, "paid off."

The diagnosis of latent syphilis is difficult, if not impossible. By definition latent syphilis is that phase of the disease in which the patient presents no demonstrable clinical evidence of syphilis after the most scrutinizing examination and shows no abnormalities in the cerebrospinal fluid. Diagnosis, therefore, rests mainly on history and the results of the serologic tests. We all recognize the unreliability of history. In addition, one has to contend with the paradoxical behavior and fluctuations of the serologic reactions in patients treated for latent syphilis

and the false results of these tests. It is not pertinent to discuss the details of what is known about biologic false serologic reactions to the tests for syphilis, but unless careful consideration is given to this factor in any series of cases of so-called latent syphilis treated with any mode of therapy the results are practically worthless. The importance of false positive reactions is further emphasized by the recent introduction of the Treponema pallidum immobilization test. If the results of this procedure are as reliable as they seem to be, it would appear, according to Moore and Mohr,[2] that false positive results are frequent, since in their practice 43% of patients in whom in earlier years latent syphilis would have been diagnosed have now been identified as biologically false positive reactors. The more extensive examinations, the more rigid serologic criteria currently available, and the more critical attitude of the practitioners would, of necessity, make for a higher percentage of real syphilis in more recently studied groups of patients and might account for the somewhat higher incidence of progression in the cases of the Epstein group treated with penicillin.

An important concept reemphasized in the present study is that, although serologic reversal is not related to the eventual outcome, progressions are more frequent in serofast cases regardless of the type of treatment. On the whole, the low percentage of serologic reversals obtained with penicillin by Epstein and his colleagues is usual for any therapy of late latent syphilis. In the past, no one system of treatment yielded a high incidence of seronegativity or rapid fall in titer. The percentage of good serologic results reported for latent syphilis is generally dependent upon the proportion of early to late latent cases in the series. The more early cases in the group, the better the results. The later cases may require years to attain seronegativity. In most instances, repeated courses of therapy have accomplished little more than the initial course. Perhaps one of the factors conditioning serologic and clinical outcome is not the duration of observation but the actual duration of the infection. Since many patients are unaware of their syphilis and may have been harboring asymptomic syphilis for many years,[3] the duration of infection as given by patients may be entirely misleading.

The meager statistics on the outcome of treated and untreated latent syphilis in the literature is due to the belief that information of value can be obtained only by follow-up studies of patients over a period of many years. Ten years, and preferably a lifetime, of observation has been thought to be necessary before one may determine the effectiveness of treatment. All the significant retrospective studies on the treatment of latent syphilis which appeared shortly before the introduction or wide use of penicillin have emphasized the lack of correlation between treatments and serologic outcome in latent syphilis (references 4, 5, and 6), a fact confirmed by the Epstein group study.

In 1948, Blum and Barnett,[7] noted that while analysis of the prognosis in latent syphilis and of the effect of treatment on it was based entirely on the frequency of clinical progression per patient-year of observation, small figures could be avoided if the incidence of relapse was multiplied by 100 and was given in terms of patient centuries of observation, designated as "per century" for the sake of brevity. According to these authors, this method of study permitted the inclusion of a large number of patients observed for short periods whose cases would otherwise have to be eliminated. This resulted in a great augmentation of the total data and provided a more representative sample of late latency. Also, it did not require the exclusion of progressions because they happened to have been noted within the arbitrary minimum time. Observation periods were computed to the nearest year; the shortest time considered was just over six months.

Blum and Barnett felt that the century-of-observation method gives a clearer conception of prognosis and of the influence of treatment than does the per capita method because it introduces the factor of time and thus furnishes some notion as to when a progression might be expected, rather than a crude estimate of the total probability of progression, provided the patient lives long enough to have one. They suggested that by the use of the proposed method of analysis it should be possible to determine the value of penicillin in latent syphilis in a few years if a large group of patients were treated, rather than in the 10 to 25 years previously thought necessary for such a study. Utilizing this method, Epstein and his colleagues have indicated the distinct advantages for the patient's future derived from therapy.

The present report by Epstein and his group, in a preliminary way, confirms this prediction in that the frequency of progression per century of observation in the relatively small series here reported is practically the same for penicillin as for adequate metal chemotherapy.

This study is provocative of a number of questions, but I shall raise only two: Since latent syphilis is a nondisabling process and since the incidence of progression is relatively low, is there any added advantage in treating patients with penicillin if they have had treatment adequate by previous standards?

Although all forms of treatment seem to yield nearly the same results, what should the therapeutic regimen for late latent syphilis be?

DR. CHARLES R. REIN, New York: It was a privilege to hear Dr. Epstein's paper. The data presented here today will serve as a basis for comparison with the results of future investigations on the effect of treatment in late latent syphilis. It was surprising and disappointing to hear that chemotherapy appeared to be more effective than penicillin therapy, in that with the latter there was a greater tendency for the development of serum resistance and therefore more progression of the syphilitic process is anticipated. Is it possible that the more rapid serologic reversal noted with chemotherapy could be due to the use of the less sensitive serologic procedures employed at that time? It is well known that as the sensitivity of tests are increased, the longer it will take to obtain seronegativity.

I should also like to ask Dr. Epstein whether he has any information regarding the incidence of serious untoward reactions in the arsenic-bismuth group as compared with the penicillin group. I agree with Dr. Epstein regarding needless retreatment in seroresistant patients who had received adequate therapy. In spite of the fact that it has been shown that persons who have received adequate chemotherapy do not require any additional therapy, I believe that any patient with latent syphilis who has never received any penicillin therapy is entitled to the protection of a course of that type of treatment.

DR. ARTHUR G. SCHOCH, Dallas, Texas: I should like to ask Dr. Epstein what the period was when the observation of these patients started in the Wassermann-fast group. Did the observation period of one year start from the beginning of treatment or at the end of treatment? If it started at the beginning of treatment, it means one thing. If it started at the end of treatment, it means something entirely different, for the same reason that it requires one year of chemotherapy—a minimum—to be adequate; so in one instance, in collecting these data on the Wassermann-fast group, he has possibly two years of follow-up in one group, namely, the chemotherapy group, as compared with one year in the penicillin-treated group. It makes a great deal of difference where he started his observation period.

The second question is, during what year or approximately what years did he close this study? I raise that question primarily for the simple reason, obvious to all of us, that in the past three or four years in particular, there has been casual and wide-spread use of all the antibiotics, particularly in addition to penicillin, all the orally administered antibiotics which we now know are all effective in the treatment of syphilis, including the narrow spectrum, orally administered antibiotic, namely, erythromycin. If this study was closed four or five years ago, I think it would probably make a good bit more difference as to how we interpret his findings than if it were, for example, closed in 1952.

DR. NORMAN N. EPSTEIN, San Francisco: I wish to thank Drs. Beerman, Rein, and Schoch for discussing this paper. Dr. Beerman made a very careful analysis of the paper, and I am grateful for his suggestions and criticisms.

There is no question but that what we called latent syphilis in the past may not have been latent syphilis. The interpretation of serologic reactions, upon which this diagnosis depends, is in a fairly complete state of confusion, owing to the introduction of the T. pallidum immobilization test. There is undoubtedly a high percentage of cases in which the diagnosis of latent syphilis was made on the basis of false positive serologic tests.

The criticism is made that we were more accurate in our diagnosis in the penicillin-treated group and that this fact may account for some of the unfavorable results reported. The sensitivity of the tests of 25 years ago was certainly less than those of today. This may also partially account for the higher percentage of seroresistance found in the pencillin-treated patients. I do not think that these criticisms invalidate the main thesis of this paper, i. e., the incidence of progression in late latent syphilis and the effect of treatment thereon. It may be that the seroresistance noted in the penicillin-treated group is not a fact, and future experience may disprove our findings.

Dr. Rein, we did not take up the question of serious reactions from arsenic and bismuth in this paper. However, we all know that they occurred not uncommonly and we do not see them after penicillin therapy.

Patients with late latent syphilis who had received previous adequate arsenic and bismuth therapy we treat with penicillin if they are seropositive. Penicillin probably acts in a manner different from arsenic and bismuth, and therefore penicillin should be given in order to assure the patient that he has had the advantage of as complete protection from his disease as possible from antisyphilitic therapy.

Dr. Schoch, the observation period in these two groups was one year from the start of treatment in both groups. Perhaps they are not comparable, but they seemed to us to be fairly so.

This project was conducted during the past three years and was supported by the Public Health Service. We were very careful to determine whether the patient had had antibiotics for any reason before starting therapy. If he had had such therapy he was excluded from the group.

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Correspondence

FATAL SHWARTZMAN REACTION DURING ANTIBIOTIC THERAPY

To the Editor:—I was quite interested in reading the article by Nelson and Braslow on Fatal Shwartzman Reaction During Antibiotic Therapy, which appeared in the September issue of the Archives. I think their explanation is very likely the correct one; and it is, I believe, important that these cases be directed to the attention of the medical profession for a variety of reasons but particularly because certain of the factors which may conduce towards the development of a Shwartzman reaction are not sufficiently well appreciated. I spoke briefly on these at the last meeting of the American Academy of Dermatology and Syphilology, and I have a paper in press in the *British Journal of Dermatology and Syphilology* which goes into these in considerable detail.

The prime purpose, however, for writing this letter is that, whereas I agree with the authors in general, I should like to point out one additional possibility that they do not seemingly consider. They state as follows:

"However, a much more likely explanation of the reaction is that advanced by Stetson and Shwartzman, who feel that the entire picture as presented in this patient could well be explained on the basis of local preparation of the infected sites by P. vulgaris, the bacteremia then provoking the reaction at these sites. The antibiotics would be incriminated only secondarily, in that they allowed the overgrowth of P. vulgaris.

While the explanation advanced could certainly be true, another possibility is that the Shwartzman reaction was produced because their patient was sensitive to the penicillin employed. It has been shown that an antigen-antibody union taking place in a patient in whom a Shwartzman preparatory site exists can cause the production of the hemorrhagic necrotic reaction at the prepared site. The mechanism and details for this are gone into in the reference already alluded to. The importance of this is that almost anybody with a systemic infection is a potential candidate for either local or generalized Shwartzman reactions. Hence, the giving of a drug to which the patient may be sensitive or for which there is some evidence that they are sensitive can be extremely hazardous procedure in that it might provoke either a local or a generalized Shwartzman phenomenon. The moral of this is probably to recall Hippocrates' first maxim, namely, *primum non nocere.*

A. Rostenberg, Jr., M.D., Chicago

Clinical Notes, New Instruments and Techniques

PRIMARY OSTEOMA CUTIS

Report of a Case

WALTER G. GASNER, M.D.
MOUNT VERNON, N. Y.

In 1948 Leider [1] reported a case of osteoma cutis secondary to acne and compared it with Hopkins' [2] case, which was also secondary to acne of long duration. Ossifying processes in the skin are indeed rare occurrences, especially when there is no history of preexisting lesions, like nevi, epitheliomas, scars, chronic inflammatory dermatoses. Prior to 1928, Hopkins [2] could find about five cases; since then eight more cases have been reported,* in only one of which was the disease reported as having been primary.

The case here reported is nearly an exact replica of Hopkins' case [2] and Leider's [1] case so far as the distribution on the face is concerned, except that the two cases mentioned above were secondary to acne while the case reported now is primary. The Table is a summary of the relevant and comparative data of the three cases. Moreover, comparison of the Figures shows further near-perfect similarity between these two cases and my own.

REPORT OF CASE

C. F., a white woman, aged 43, a bookkeeper, presented an eruption on the face of 15 years' duration. She had been to many dermatologists, who told her that she had milia, and after a few unsuccessful attempts at removal the patient sought help elsewhere.

Dermatologic examination revealed discrete papules scattered about the face varying in size from pinpoint to pinhead, some of which were more deeply embedded in the skin. The color varied from skin color to yellowish-white. One could easily palpate the individual lesions. Insertion of a needle into one of these papules was met with stone-like resistance.

There was no history of any previous acne or dermatologic condition. The patient merely stated that these "tiny bumps" had appeared during the past 15 years.

X-ray examination of the skin of the face uncovered many tiny radiopaque (calcific) shadows in several places (Fig. 1).† A biopsy of the cheek showed bone formation in the cutis (Fig. 2).‡

COMMENT

For many years this patient had been seen by various dermatologists, who told her that she had milia and attempts were made to remove them; however, considerable difficulty was encountered, and the patients decided to allow the condition to be left untreated.

I attempted to remove one of the lesions with a 26-gauge hypodermic needle and met with stone-like resistance, which convinced me that performance of a biopsy was the next procedure.

The pathogenesis of osteoma cutis in this case, in my opinion, is one of embryonal cell rests of osteoplastic elements or a type of a nevus tardus.

The other two types of ossifications, namely (1) metaplastic ossification secondary to chronic inflammatory processes and other preexisting irritative states, and (2) neoplastic ossification, do not fulfill the requirements of this case.

* References 3 to 8.

† Dr. William J. Gersh made the X-ray studies.

‡ Dr. Wilbert Sachs made the pathologic examination.

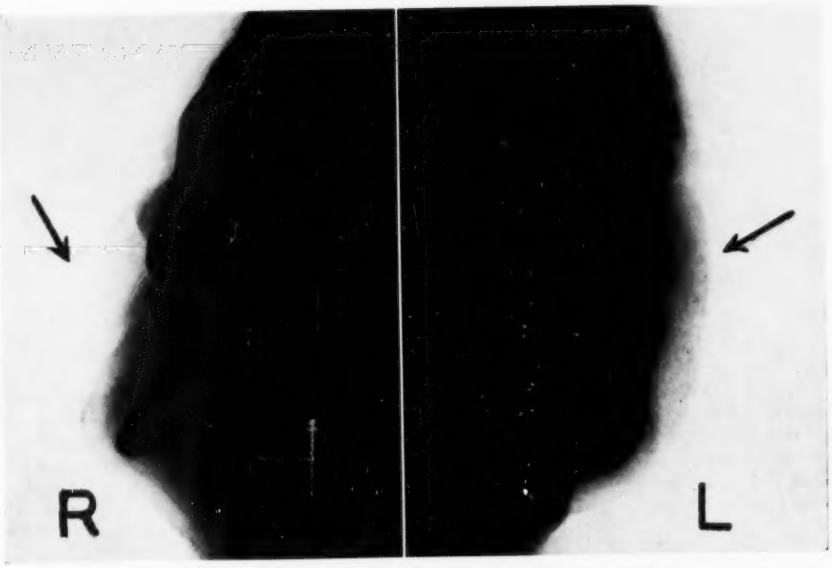

Fig. 1.—Reproduction of roentgenogram, soft-parts technique.

Fig. 2.—Photomicrograph of a section of the skin showing osteomas in situ (× 75).

Comparative Data in Three Cases of Osteoma Cutis

Data	Hopkins' Case	Leider's Case	Case Described Here
Age, yr.	44	34	43
Dermatologic history	Acne, 10 yr. duration, onset at age 30; comedones, papules, pustules, scars	Acne, 21 yr. duration, onset at age 13; comedones, papules, pustules, scars	None
Previous dermatologic treatment	X-rays, vaccines, diet, topical remedies	X-rays, vaccines, ultraviolet rays, diet, topical remedies	None
General medical history	"Many indefinite conditions, nature of which could not be determined"	Many indefinite conditions, nature of which indeterminable by extensive medical work-up	Essentially normal
General condition	Essentially normal	Essentially normal	Essentially normal
Psychiatric opinion	"Somewhat neurotic"	Decidedly neurotic	Essentially normal
Laboratory observations	Blood cell count: r. b. c. 4,460,000, w. b. c. 5,600, normal diff. count; normal urine; blood chemistry (mg./100 cc.): calcium 10.8, sugar 107.1, urea nitrogen 13.04, chlorides 495, cholesterol 250, phosphates not determined; basal metabolic rate —19%	Blood cell count: r. b. c. 4,410,000, w. b. c. 6,800, normal diff. count; normal urine; blood chemistry (mg./100 cc.): calcium 11.8 (normal 9.6-11), sugar 85 (normal, 80-120), urea nitrogen 14 (normal, 10-15), chlorides 445 (normal, 450-500), cholesterol 135 (160-230), phosphates: specimen hemolyzed 3.5-4; basal metabolic rate —16% (1941), —10% (1947)	Blood cell count: r. b. c. 4,400,000, w. b. c. 7,100; diff. count: neut. 52%, lymph. 46%, mono. 2%; cholesterol 270 mg.; basal metabolic rate —6%
Size of recovered osteomas	0.5-2 mm.	0.5-1.5 mm.	0.5-1.5 mm.
No. of recovered osteomas	30-50	12	75
X-ray observations of soft parts	Not made	Multiple minute soft-tissue calcific deposits in skin of the chin, around the nose, and brow (Dr. W. H. Meyer)	Multiple small intracutaneous and subcutaneous calcified nodules in soft tissues of both cheeks, chin, nose, and brow (Dr. W. J. Gersh)
Cell structure of specimen	Lamellated in concentric rings; numerous lacunae, most of which contained stainable nuclei; one of two Haversian canals seen containing small vessels; specimen in situ	Concentric arrangement of structure showed numerous lacunae containing stained nuclei, which gave the impression of being those of osteoblasts; specimen not in situ; this appearance occurs whether or not the specimen are in situ (Dr. M. N. Richter)	Lamellated in concentric rings; numerous lacunae, most of which contained stainable nuclei; Haversian canals present

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REMOVAL OF STAINS OF POTASSIUM PERMANGANATE

ROBERT J. MORGAN
AND
RAY M. BALYEAT
OKLAHOMA CITY

Most physicians are at times faced with the problem of having their patients remove the stains of potassium permanganate. It has been such a problem that many physicians have failed to prescribe it for that one factor, even though some dermatologists maintain that it is the most effective single medicine that can be used in acute dermatoses. A simple, safe, and entirely satisfactory means of removing the stain has been found.

One of our recent patients who had used potassium permanganate in caring for poultry laughed at our apologies at prescribing the soaks and said that removal of the stain was no chore. She said that her mother had told her to make a fresh mixture of cream of tartar (potassium bitartrate) and hydrogen peroxide, both common household materials, so that a thin paste is made. When this mixture is applied to the stain, the latter will vanish with the ease with which chalk can be erased from a blackboard.

The "Physicians' Desk Reference" for 1952 advised the use of dilute 2% sulfurous acid, dilute hydrochloric acid, oxalic acid, sodium thiosulfate (Hyposulfite), or alkaline sulfates, or lemon juice. For fabrics, it advises first washing with ammonium sulfate solution, and the resulting manganese sulfate is dissolved with a 10% solution of potassium cyanide. All these materials have their disadvantages. They are either difficult to obtain, or dangerous to use, or injurious to the skin, enamel, metal, etc., or, in my experience, do not work. The mixture of potassium bitartrate and hydrogen peroxide was applied with a soft cloth or cotton to enamel containers, skin, finger nails, toe nails, and cloth, and in all instances the stain immediately vanished and did not return. For fabrics we found that sprinkling potassium bitartrate over the stained area, then pouring on or rubbing the cloth with cotton soaked in hydrogen peroxide was the easiest way. It may be assumed that some clothing dyes may not withstand this mixture, but so far we have not seen any unwarranted bleaching by the peroxide.

Why does this work when common solvents, scouring soaps, and detergents fail? In trying to answer this question, we tried the following materials, and none worked with any degree of success; hydrogen peroxide alone, potassium bitartrate alone, antimony potassium tartrate (tartar emetic) alone and with hydrogen peroxide, Seidlitz powders alone and with hydrogen peroxide, and bismuth potassium tartrate alone and with hydrogen peroxide.

It was found that plain tartaric acid with hydrogen peroxide works equally well, and the only advantage of potassium bitartrate is its availability.

Dr. Mark Everett, Biochemist and Dean, University of Oklahoma School of Medicine, suggested that the following might explain the reaction:

Probably the brown stain is due to manganese dioxide or a hydrate. Such substances can be reduced by hydrogen peroxide in acid solution. In the presence of hydrogen peroxide and manganese ions, tartaric acid is oxidized. Probably the oxidation of the organic acid plays a necessary role in a coupled reaction to cause effective reduction of the stain.

ALLERGIC ECZEMATOUS CONTACT-TYPE DERMATITIS DUE TO ZORIS

CAPTAIN M. PAUL LAZAR
MEDICAL CORPS, UNITED STATES ARMY

Allergic eczematous contact-type dermatitis has been reported to have been due to many common and unusual objects. The following case is being reported because many servicemen and their dependents, as well as increasing numbers of world travelers, will be returning to the United States using objects which have become an integral part of their daily lives.

From the Medical Service, Osaka Army Hospital.

One such type of apparel are zoris, a type of Japanese footgear which is being worn commonly by thousands of Americans living in and returning from the Far East. These are made of various materials, including rubber, rice straw, leather, and wood, with numerous materials being used as retaining straps.

REPORT OF A CASE

A 22-year-old white sergeant, R.L.B., was referred to the dermatology clinic, Osaka Army Hospital, with a diagnosis of dermatophytosis. Two weeks prior he had noticed the onset of a dermatitis on the dorsum of the small toe of his left foot. Thinking this to be a fungous infection

Fig. 1.—These blue rubber *zoris* were implicated in the reported case.

he applied foot powder. Four or five days later a vesicular eruption became apparent on the palmar aspects of the hands, as well as on the lateral surfaces of the fingers. He reported to his local dispensary from which he was referred to our clinic.

When I saw the patient, his condition was confined to his hands and feet. The lesions were vesicular and bullous in nature, studded on an erythematous base, with one small eczematous area on the lateral surface of the small toe of the left foot. A well-demarcated erythematous area extended from and included the interspace between the first two toes on each foot. The eruption spread in a V-shaped arrangement over the dorsum to a point on each side of the foot just anterior to each malleolus. The eczematous area was studded with tense vesicles

and bullae, as were both soles except for the area of the longitudinal arch. In addition, covering both hands were many vesicles and bullae, these being severer on the hypothenar and thenar eminences, as well as on the lateral aspect of the fingers.

Questioning revealed that this man wore blue rubber zoris as house and shower shoes. Subsequently, patch tests done by conventional methods elicited a vesiculobullous response to the rubber material used in construction of the zoris. It was impossible to ascertain which particular ingredient, including the coloring agent of the rubber, was the offending agent. Several control tests gave no abnormal response. When the zoris were discarded the patient's hands and feet returned to normal.

No fungi were found on repeated examinations during the height of and after the subsidence of the eruption.

It was interesting to once again note an id-like reaction on the hands secondary to a foot eruption not mycotic in origin. This tends to support the theory of the occurrence of distant dermatoses thought to be due to local absorption followed by hematogenous spread, as one rarely handles zoris in putting them on one's feet.

SUMMARY

A case of allergic eczematous contact-type dermatitis due to rubber zoris is reported.

MALIGNANT MELANOMA

JOHN F. MADDEN, M.D.
ST. PAUL

A case of malignant melanoma is presented because of the unusual manner in which the malignant melanoma metastasized. When malignant melanomas metastasize to lymph nodes, they usually metastasize to the nodes that drain the area in which the tumor is situated without showing any perceptible involvement of the intervening skin. In this patient, the melanoblasts followed the superficial lymphatics over the ilium to the pubic region before the inguinal lymph nodes were palpable (Figs. 1 and 2).

Mohs and Lathrop [1] recently stated that some cancers show a peculiar affinity for some specific tissue structure, which they follow selectively for unexpectedly great distances. They enumerated the following structures which certain cancers showed particular affinity for: (1) dermis, (2) fascial planes, (3) periosteum, (4) perichondrium, (5) embryonic fusion planes, (6) nerve sheaths, (7) lymphatic vessels, and (8) blood vessels. The malignant melanoma herein reported showed an affinity for lymphatic vessels.

REPORT OF A CASE

A. C., a 74-year-old white man showed a dime-sized, ulcerated, painless, pigmented nodule on the right buttock, of questionable duration. A biopsy was performed on Jan. 21, 1952, and the microscopic section showed malignant melanoma. The tumor was widely excised on Jan. 30. Metastatic lesions began to appear along the superficial lymph channels shortly after the excision. Later, metastatic lesions were also found in the rectum, colon, and lungs. The patient died in August.

SUMMARY

An example of malignant melanoma is presented whose metastasis in part showed a particular affinity for lymph vessels.

REFERENCE

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From the Department of Dermatology and Syphilology, Ancker Hospital, Dr. John F. Madden, Director; and the Division of Dermatology and Syphilology, University of Minnesota Medical School, Dr. H. E. Michelson, Director.

Fig. 1.—Scar at site of malignant melanoma and metastatic lesions following superficial lymph vessels anteriorly over the ilium.

Fig. 2.—Metastatic melanoma following the superficial lymphatics to the inguinal lymph nodes.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Rudolf L. Baer, M.D., President

Henry Silver, M.D., Secretary

March 19, 1953

Erythroplasia of Queyrat Treated with Thorium X. Presented by Dr. Victor H. Witten and Dr. Abraham J. Orfuss.

E. M., a white man aged 67, was first seen at the skin and cancer unit of the University Hospital, New York University Post-Graduate Medical School, on June 10, 1952. He gave a history of a lesion on the penis which had been present for one year.

On examination there was a 6 by 10 mm., oval, sharply defined, red, glistening, slightly elevated plaque on the shaft of the penis just proximal to the coronal sulcus. There was no regional lymph node involvement. The result of a biopsy taken from this area was erythroplasia.

The area was first treated with thorium X (300 μc per cubic centimeter of alcohol) applied locally on June 26. The second treatment was given on July 10. Because of marked erythematous response treatment with thorium X was discontinued. Definite improvement was noted, and treatment was interrupted.

On Sept. 4, there was a recurrence in the same area. It was not until Nov. 6 that thorium X treatments were again started. Three additional treatments were given at weekly intervals (for a total of five), but were discontinued (Nov. 20) because of marked erythematous response and maceration.

On Jan. 8, 1953, the area was completely healed and has remained healed until the present time.

Histologic examination by Dr. Charles F. Sims showed an irregularly acanthotic epidermis. There was a marked downward projection of the rete pegs. The cells of the epidermis showed mild irregularity. Some of the cells were large and hyperchromatic. Mitotic figures were present. A parakeratotic scale covered the epidermis. There was a marked inflammatory reaction in the upper cutis consisting mainly of plasma cells.

DISCUSSION

Dr. Earle W. Brauer: If the diagnosis is correct and one notes the response of this pathologic process to thorium X therapy, it serves to explain the effectiveness of this modality. The radioactivity of thorium X is absorbed by the epidermis and superficial layers of the corium. This is another form of getting effective radiation to a superficial pathologic process.

Dr. William Siskind: Was Dr. Sachs's method of treatment tried?

Dr. Arthur B. Hyman: The condition erythroplasia can be divided into two groups, these being (1) on the penis of circumcised males, and (2) that occurring on the semimucosa of the penis of the uncircumcised. It would be reasonable to expect that those patients circumcised shortly after birth would not develop premalignancies, and that these cases should be differentiated from the group with lesions that we call erythroplasia, and which more possibly and potentially may be premalignancies. I am not in a position to say now whether there is a clear histological differentiation, but I do think there is a measure of parallelism. In lesions seen in the circumcised there is a histological picture hardly characteristic and not diagnostic, and the vast majority of sections labeled erythroplasia cannot, I believe, be so diagnosed just by looking at the slides. On the other hand, it is possible that lesions of erythroplasia in the uncircumcised do have definite features and may possibly be considered as being Bowen's disease of the semimucosa, as was postulated by Civatte. The slides seen tonight in the erythroplasia in an uncircumcised man have the features of intradermal, basal-cell epithelioma, so that, for the time being, I would accept this case as one of the variants of erythroplasia. The result with thorium X is an excellent one, and we would all agree to the plausibility of Dr. Brauer's explanation.

DR. NATHAN SOBEL: At another dermatological society, several years ago, the evening was spent on the discussion of erythroplasia. Everyone agreed that there was no report in the United States of erythroplasia eventuating in carcinoma. Dr. Andrews stated that he had seen possibly one case which may have been carcinoma at its onset. The final consensus was that the cases diagnosed as erythroplasia in this country are not the same type as those formerly described by Queyrat, even though the cases we see here resemble those clinically. The histological findings are likewise similar to those described by Queyrat.

DR. CHARLES GRUPPER, Paris, France (by invitation): In France, our concept of erythroplasia corresponds to yours. It is regarded as an intraepidermal type of epithelioma and is treated as such.

DR. VICTOR H. WITTEN: We are now treating a case of Bowen's disease of the finger at Skin and Cancer Unit, and after four weekly applications of thorium X there has been considerable improvement. Additional treatments will be given, and we shall therefore have to wait to see the eventual outcome. In answer to Dr. Siskind, we did not use the Sachs method of treatment. The question of diagnosis of erythroplasia continues to be a problem. What Dr. Hyman said tonight fits in with the clinical evidence cited by Dr. Sobel. Several years ago, I heard Dr. MacKee and Dr. Sulzberger discuss the prognosis of lesions of the glans, which had been diagnosed as erythroplasia. They both stated that they had never seen a case of erythroplasia, which they had followed in this country, eventuating in carcinoma. They were not certain whether the patients were circumcised or uncircumcised, but thought that the majority, at least, had been circumcised. This, they said, was quite at variance with what has been seen in European countries, and they speculated as to whether or not the difference in course and outcome had any relationship with being circumcised or not being circumcised.

When the diagnosis is questioned clinically or histopathologically and when the lesions fail to respond to other forms of therapy the patient should have a trial with thorium X. Of course, many more cases will have to be treated in order to properly evaluate this modality.

Urticaria Pigmentosa. Presented by DR. NATHAN SOBEL.

DISCUSSION

DR. CHARLES GRUPPER, Paris, France (by invitation): After reading the papers of Sagher and his colleagues and Clyman and Rein (Sagher, F.; Cohen, C., and Schorr, S.: *J. Invest. Dermat.* **18**:425, 1952, and Clyman, S. G., and Rein, C. R.: *J. Invest. Dermat.* **19**:179, 1952) I had the opportunity to restudy nine patients with urticaria pigmentosa for the presence of bone lesions. In three, one child and two adults, bone lesions were observed similar to those reported by Sagher and his colleagues and Clyman and Rein. These lesions were calcified infiltrations as illustrated in the paper by Clyman and Rein. Unfortunately, we were not able to obtain a biopsy of the bone lesions. It is likely, however, that the bone lesions represent collections of mast cells, because bone lesions have been found by Ellis (Ellis, J. M.: *Arch. Path.* **48**:426, [Nov.] 1949) in an infant who had generalized urticaria pigmentosa. From an etiological standpoint, Ellis also speculated on the relationship of gonococcal cervicitis, which was present in the mother of the infant, with urticaria pigmentosa on autopsy. Recently, I have seen three newborn infants in whom it was possible to prove the existence of gonococcal cervicitis in the mothers. Professor Degor and Professor Duperrat have also found two cases of urticaria pigmentosa in newborn infants with mothers who had been infected with gonococcal cervicitis. In order to establish the relationship, we are undertaking a study of the mothers of children with urticaria pigmentosa. Also, we are examining the cervix for PPLO (pleuropneumonia-like organisms).

DR. ALEXANDER A. FISHER: In a young girl with urticaria pigmentosa proved by histologic examination I prescribed calciferol because of the resemblance to guttate parapsoriasis. Much to my surprise there was considerable improvement of the eruption while the patient was being given the drug. When the calciferol was omitted the eruption recurred and when the calciferol was reintroduced there was again improvement. I suggest that this therapy be given a trial in this disease.

DR. NATHAN SOBEL: It is being recognized more and more that urticaria pigmentosa is a systemic disease, and mast cells may be found in all organs of the body. In one recorded autopsy of this disease, mast cells have been found in the various organs—liver, spleen, bone, marrow, muscles, and most of the organs of lymphoid nature. Is the origin of the mast cell perhaps

reticuloendothelial? Dr. Pascher is of the opinion that it possibly may arise from mesodermal tissue. The granules in the mast cells have been reported as being heparin. There is no increase in coagulation or bleeding time in this patient and other reported patients.

Recurrent Bowen's Disease Treated with Grenz Rays (Ultrasoft Roentgen Rays). Presented by Dr. Earle W. Brauer.

Multiple Superficial Epitheliomatosis and Bowen's Disease? Presented by Dr. Irwin I. Lubowe.

Epidermolysis Bullosa. Presented by Dr. Hans H. Biberstein and Dr. Sidney G. Clyman (by invitation).

Crossed Hemihypertrophy. Presented by Dr. David Bloom.

Case for Diagnosis (Alopecia Traumatica? Alopecia Areata? Follicular Hyperkeratosis? Presented by Dr. Frances Pascher, Dr. Andrew G. Franks, and Dr. Ernst Rosenbaum (by invitation).

Dermatitis Occurring in Extremity Enlarged Due to Arteriovenous Fistula; Acromegaly. Presented by Dr. Abraham J. Orfuss.

Annular Sarcoid with Severe Secondary Anemia. Presented by Dr. Alexander A. Fisher.

Acrodermatitis Chronica Atrophicans. Presented by Dr. Alexander A. Fisher.

Case for Diagnosis (Contact Dermatitis? Photosensization Phenomenon?). Presented by Dr. Abraham J. Orfuss.

Exfoliative Dermatitis with Involvement of Mucous Membranes. Mycosis Fungoides? Presented by Dr. Alexander A. Fisher.

Case for Diagnosis (Nodular Neurodermatitis? Lichenoid Dermatitis Due to Gold?). Presented by Dr. Abraham J. Orfuss.

Dermatitis Factitia. Presented by Dr. Nathan Sobel.

Subacute Disseminated Lupus Erythematosus? Presented by Dr. David Ballin.

Acrodermatitis Chronica Atrophicans (Early Stage). Presented by Dr. Irwin I. Lubowe and Dr. Sidney G. Clyman (by invitation).

Rudolf L. Baer, M.D., *President*

Henry Silver, M.D., *Secretary*

April 16, 1953

Palmar Erythema with Hyperhidrosis. Presented by Dr. Abraham J. Orfuss.

I. W., a man aged 49, noticed about three years ago that the sides of his palms were diffusely red. For the past few months there has been increased sweating of the palms under nervous stress. For the past year the patient noted mottled redness at the angles of the jaws. There are no constitutional symptoms.

Physical examination shows a palpable liver. There is symmetrical palmar redness of the thenar and hypothenar eminences. Hyperhidrosis of the palms is marked. The angles of the jaw present multiple telangiectasis and dusky pigmentation.

The urine was normal. The serologic reactions for syphilis were negative. The prothrombin time was 18 seconds undiluted, 52 seconds diluted (12 to 18) (35 to 42). The thymol turbidity test was 1.0 unit (0.4). The icterus index was 7.1 (4 to 6). The cephalin flocculation test was 0 (0 to 2). Complete examination of the blood gave normal findings. The blood cholesterol was 205 mg. per 100 cc. of blood (160 to 230). The sedimentation was 8 mm. in one hour (10). The electrocardiogram showed "clock-wise rotation of the heart; no other changes of significance."

DISCUSSION

Dr. Paul Gross: What was the serum protein in this case? Hyperproteinemia has been described in these cases. It may very well be a sarcoidosis of the liver.

Dr. Franz Herrmann: The distribution of hyperhidrosis in the axillary fossae and the palmar surfaces of this patient might appear suggestive of excessive "emotional sweating." There are, however, several features which appear to indicate that this hyperhidrosis may result also from other factors. Aside from the fact that increased sweating was not noticeable until about three years ago (which would be unusually late for the beginning of "emotional hyperhidrosis"), the history reveals a marked susceptibility of his axillary and palmar sweat glands to stimulation by heat. The condition is much more pronounced during the summer. The patient himself is wondering "why he does not sweat" in any areas except in the armpits and on the palms and soles, especially at high environmental temperature. We know that thermogenic hyperhidrosis may be confined to these areas in exceptional instances. It appears worth while

to test this patient by exposure to dry heat, since it has been our experience that thermal stimulation results in a measurable increase of thermogenic hyperhidrosis of the palms, whereas there is no such increase in emotional hyperhidrosis.

To a large extent, the excessive sweating of Dr. Orfuss' patient might be adrenergic. He shows distinct features of hyperthyroidism, such as exophthalmus, firm swelling of the thyroid gland, and weight loss. For the understanding of thyrotoxic hyperhidrosis one must consider not only the generally increased emotional sensitivity of these persons, but also the increased basal metabolic rate, which would lead to excessive accumulation of heat in the body unless there is compensatory heat dissipation by augmented sweating. Regarding treatment, we obtained favorable results with benzazoline (Priscoline) in similar forms of hyperhidrosis.

Evidently, a severe systemic disorder (Hodgkin's granuloma?) is the general factor underlying the manifestations observed in this patient.

DR. ABRAHAM J. ORFUSS: This condition is described as being associated with liver disease, and when we referred the patient to the medical clinic for work-up, liver enlargement equivalent to three fingerbreaths below the costal margin was found. However, there were no other clinical signs associated with liver disease; liver function tests were all found to be within normal limits.

Keratosis Pilaris Atrophicans Faciei (Brocq). Presented by DR. ALEXANDER A. FISHER and DR. MAX WOLF (by invitation).

F. T., a girl aged 6½ years, presents a pigmented mole on the left inner aspect of the upper arm and a pigmented spot on the left breast. Beside pigmented nevi, there are reddish papules on the face which according to the mother were first seen by her about four years ago.

On the outer parts of the cheeks and in the parotid region the skin is diffusely red granular and covered by closely set round follicular keratotic papules or plugs, the size of a pinhead. On the upper lip there are a group of whitish hard round papules. On the chin there are a group of similar lesions. The rim of the helices is studded with tiny yellowish papules. On the outer aspect of the upper arms there are typical lesions of keratosis pilaris.

Keratosis Pilaris Atrophicans Faciei (Brocq). Keratosis Pilaris. Presented by DR. ALEXANDER A. FISHER and DR. MAX WOLF (by invitation).

G. P., a girl aged 10 years, has had white spots on the face for the past five years. The condition has become worse in the last two years.

On both cheeks and in the temple regions there are widely disseminated discrete follicular round hard papules resembling milia, the size of a pinpoint or pinhead. The follicles of the nose are filled with pinpoint dirty grayish plugs. On the right upper part of the forehead there is a brownish patch with prominent follicles. On the left cheek near the mouth there is an atrophic spot. The rims of the helices are studded with closely set yellowish papules the size of a pinhead. Both ear lobes show tiny whitish papules. On the outer upper arms there are follicular conical or flat papules the size of a pinhead to matchhead.

Keratosis Pilaris Atrophicans Faciei (Brocq). Keratosis Pilaris. Presented by DR. ALEXANDER A. FISHER and DR. MAX WOLF (by invitation).

H. T., a girl aged 15 years, states that since the age of 8 years the skin has been dry, rough on the arms and thighs. The scalp was dry and scaly.

On the outer aspect of the upper arms, thighs, and buttocks there are typical lesions of keratosis pilaris. On the face there are closely set follicular keratotic papules, the size of a pinhead, and tiny atrophic spots.

DISCUSSION

DR. NATHAN SOBEL: I had recently under my observation a similar case with involvement of the eyebrows resembling the clinical picture of ulerythema ophryogenes.

DR. MAX JESSNER: This syndrome belongs in the group of congenital follicular lichen pilaris. These cases present some redness and edema which places them in a well-defined group.

DR. JOHN GARB: Have vitamin A studies been done on these children?

DR. PAUL GROSS: Have any of the members had any experience with the local application of female sex hormones?

DR. MAX WOLF (by invitation): These cases are not often described in the American literature. The first case was recorded in 1889. I do not think the disease can be influenced by vitamin A, even in large doses; it disappears with age. P. J. Unna described cases in which erythema was present but was associated with loss of hair in the eyebrows and much more atrophy than exists in the present cases. Many authors are of the opinion that the cases that I presented comprise a distinct entity and bear no relationship to Unna's disease.

DR. ALEXANDER A. FISHER: Since Dr. Wolf brought these cases to my attention, I reviewed the literature available to me and found a great deal of confusion. Some feel that keratosis pilaris atrophicans faciei and ulerythema ophryogenes are similar; others are of the opinion that these are two distinct entities. My personal feeling is that the cases presented are distinct from keratosis pilaris and from ulerythema ophryogenes.

Pemphigus Vulgaris Complicated by Diabetes, Apparently Cured (?) with Corticotropin (ACTH) and Cortisone. Presented by DR. DAVID BLOOM.

L. F., a woman aged 54, was previously presented at the Manhattan Dermatological Society on April 8, 1952, and Feb. 10, 1953.

DISCUSSION

DR. CLINTON H. MARTIN: We have used corticotropin (ACTH) with good results in some cases and cortisone with no results whatsoever. In some cases when cortisone failed, the lesions cleared with corticotropin. I should like to hear what the experience of others has been with these drugs.

DR. MAURICE UMANSKY: Was the presented case a severe form of pemphigus vulgaris verified by biopsy or was it the mild type? The prognosis in the latter condition is not grave, and better results are to be expected.

DR. PAUL GROSS: After reviewing the history of this case one is impressed with the skillful handling of the therapy in view of the complicating factors. Despite the complete remission without further steroid hormone therapy I have no doubt about the diagnosis of pemphigus vulgaris.

DR. MORRIS LEIDER: I can report similar instances of severe pemphigus brought into remission with either corticotropin or cortisone and kept in remission. In the two cases I have under observation, one, pemphigus vulgaris, after three years, requires 30 mg. of corticotropin daily, and the other, a case of pemphigus vegetans, which in the hospital showed the features of pemphigus vulgaris, was controlled with corticotropin, discharged with cortisone, maintained free of lesions with cortisone, and now, for one month, with no cortisone therapy, is still free of lesions.

DR. DAVID BLOOM: The difference in results reported between cortisone and corticotropin is due to the fact that in order to obtain the same result as from corticotropin two and one-half times as much cortisone must be given. One has also to consider that in some patients or in the course of an illness in the same patient the requirement for corticotropin or cortisone may change, and a much larger dosage is needed. Although usually corticotropin may be substituted for cortisone and vice versa, with the same effect, I believe that there are situations in the course of illness when corticotropin may act better than cortisone. Theoretically, this may be in some instances explained by the response of the adrenal cortex or by the lack of response to the hormone. In this patient, presented tonight, no cortisone has been given in the past five months. Except for an occasional small bulla which dries up rapidly, there was no recurrence. It is conceivable that this patient is cured of the pemphigus.

Mycosis Fungoides, Tumor Stage, Treated with Corticotropin and Cortisone. Presented by DR. JOHN GARB and DR. JOSEPH SILVERBERG (by invitation).

F. K., a man aged 50, was hospitalized for the fourth time in the University Hospital from Oct. 22, 1952, till Jan. 9, 1953. The symptoms began in 1945 with a generalized pruritus. In 1947 skin lesions appeared, diagnosed as mycosis fungoides, and verified by repeated biopsies.

He has been variously treated with nitrogen mustard, x-ray, and thorium X, including supplemental supportive therapy of vitamins, diet, and blood transfusions. These modalities all resulted in temporary remissions of varying degree but exacerbations always occurred in varying periods of time. He was hospitalized on this occasion because of weight loss and anemia and in order to initiate a new therapeutic regimen.

On physical examination, he appeared undernourished and had severe generalized pruritus. The chest and heart were normal; liver edge was palpable two fingers below the costal margin. There was generalized lymphadenopathy and bilateral ankle edema. The skin was generally infiltrated, lichenified, and excoriated. The lesions consisted of three types: (1) small erythematous excoriated crusted papules, (2) large irregular raised erythematous infiltrated scaly plaques, and (3) large raised nodular tumors, particularly on the forehead, scalp, and neck.

On admission, the hemoglobin was 8.3 gm. per 100 cc. of blood, and there were 2,900,000 erythrocytes per cubic millimeter. Three transfusions of 500 cc. of blood each were given, after which his hemoglobin rose to 12.2 gm. and the erythrocytes to 4,100,000 per cubic millimeter.

The urine showed consistently the presence of microscopic red blood cells, and after genitourinary consultation it was decided that this was most likely due to renal involvement by the primary disease.

The patient was treated with Pentamidine, 1 mg. per pound of body weight intramuscularly every other day for eight injections, at which time there developed a severe cellulitis of the face, high spiking fever, and a drop in hemoglobin and red blood cells. He was given penicillin for two days, with little effect, and then given oxytetracycline (Terramycin). In 48 hours he was afebrile and remained so. Blood cultures had been negative.

He was then started on corticotropin gel therapy, 80 mg. daily for seven days, and then the dose was gradually decreased to 20 mg., and cortisone, started at 400 mg. daily, with the dose gradually being reduced to 150 mg. On the second day of corticotropin therapy there was a diminution in the general infiltration of the skin and a marked reduction in the pruritus. There was little, if any, effect on the larger tumor nodules. He continued to improve for several weeks with this therapy.

The tumors and the infiltrated plaques were treated simultaneously with high-voltage filtered x-ray, with success in the former only. He had over 20 localized areas treated.

On the ninth day of corticotropin therapy, there developed polyuria, glycosuria, and hyperglycemia, accompanied by weight loss. This was eventually controlled with NPH insulin in the morning and regular insulin in the evening. Oxytetracycline was also given prophylactically while he was being given corticotropin, but there developed numerous pustules in spite of this. As the dose of cortisone was decreased the pruritus gradually intensified and new small nodules developed.

The patient received in addition supportive therapy such as vitamins, iron, aminoacetic acid (Glycine) and KCl. Steroid therapy was given for a total of 58 days. He was discharged on 150 mg. of cortisone daily, NPH. insulin 35 units every morning, and regular insulin 20 units every evening.

His condition has been much improved while he was in the hospital. The pruritus, which was his chief complaint, has been reduced a great deal.

DISCUSSION

DR. NATHAN SOBEL: I followed this man for a time, while he was in the hospital several months ago, when he was running a high temperature and was in a critical state. Penicillin was given because of secondary infection, following which the condition regressed. Corticotropin was then introduced, in spite of the fact that he is diabetic. With corticotropin, antibiotics, and high vitamin dosage he kept on improving. Roentgen therapy was employed for the large masses. While corticotropin is not a cure for mycosis fungoides, it is valuable symptomatic treatment and will control the disease for a while. The Veterans Administration reports show that x-ray is superior to corticotropin in the treatment of mycosis fungoides.

DR. JOHN GARB: Dr. Sobel has already stated the pertinent facts in this case. The patient was already treated with 100 mg. of corticotropin a day, with striking but only temporary results. There was rapid recurrence of the lesions one week after the corticotropin was discontinued or

reduced to 25 mg. a day. Our purpose was to give corticotropin at first and follow with cortisone therapy on the dose which may keep him fairly comfortable and prolong his life, thus enabling us at the same time to try other therapeutic measures. (Von R. Schuppli: Über die Wirkung von Cortison in zwei Fällen von Mycosis fungoides, *Dermatologica* **103**:209, 1951, and Tulipan, L.: Failure of ACTH [Adrenocorticotropic Hormone] in the Treatment of a Case of Mycosis Fungoides, *J. Invest. Dermat.* **15**:349 [Nov.] 1950).

Microsporum Audouini Infection of the Pubic Area. Presented by Dr. Andrew G. Franks and Dr. Claire L. Taschdjain (by invitation).

Sarcoid. Presented by Dr. Nathan Sobel and Dr. A. I. Weidman (by invitation).

Case For Diagnosis (Liviedo Reticularis with Nodular Vascular Changes?). Presented by Dr. Irwin I. Lubowe.

Case For Diagnosis (Parapsoriasis? Mycosis Fungoides?). Presented by Dr. David Ballin.

Mycosis Fungoides and Herpes Zoster. Presented by Dr. Julius H. Pollock.

Neurotumor (Plexiform Neuroma?) of the Right Index Finger. Presented. by Dr. Hans H. Biberstein.

Recklinghausen's Disease Treated with Electrodesiccation (Two Cases). Presented by Dr. John Garb and Dr. Irwin I. Lubowe.

Erythema Annulare Perstans (Wende)? Erythema Annulare Centrifugum (Darier)? Presented by Dr. Alexander A. Fisher and Dr. Max Wolf (by invitation).

Case for Diagnosis (Chronic Benign Familial Pemphigus?) (Hailey-Hailey?) Keratosis Follicularis (Darier?). Presented by Dr. Abraham J. Orfuss.

CLEVELAND DERMATOLOGICAL SOCIETY

Irving L. Schonberg, M.D., *President*

John R. Haserick, M.D., *Secretary*

George M. Stroud, M.D., *Reporter*

March 26, 1953

Diabetes Mellitus with Pretibial Capillaritis and Hemosiderin Pigmentation. Presented by Dr. John E. Rauschkolb and Dr. Gilbert H. Barnes.

J. W., a 19-year-old white woman diabetic, was first seen on Sept. 10, 1952, because of a mottled brown pigmentation of the legs of 15 months' duration. The eruption first appeared over the dorsa of the feet in the form of clusters of punctate, pin-head-sized red macules, which enlarged peripherally, becoming brown and later fading to lighter shades of brownish-yellow. There has been a bilateral, progressive spread of the eruption up the pretibial, lateral, and medial sides of the legs, sparing the posterior aspects entirely. Crops of new lesions have followed the same pattern, appearing first as grouped punctate red dots, which spread peripherally as the color changed to brown and brownish-yellow, with confluence of many adjacent lesions. Minor trauma has often been associated with the appearance of new lesions. The only symptom has been occasional mild pruritus. The patient has been a known diabetic for the past two years and is maintained at present on 54 units of insulin daily. She has had occasional mild insulin reactions but never episodes of insulin shock or diabetic coma. In addition, she has taken pancreatin, ascorbic acid, and rutin during the past year.

There is a symmetrical, mottled, brown-and-tan macular eruption of discrete and confluent areas of pigmentation with fairly well defined borders, localized on the legs from the ankles to the knees, appearing chiefly over the pretibial areas, with extension to the lateral and medial sides. Close examination reveals occasional reddish puncta scattered through the eruption. There does not seem to be any definite tendency for these small lesions to be grouped at the margin of the larger brown macules. The upper extremities do not exhibit any lesions of a similar nature, and the rest of the physical examination is essentially normal. Fundoscopic examination reveals normal fundi, without signs of hemorrhage or exudate.

Repeated urinalyses revealed a 4+ sugar, negative albumin, and negative microscopic results. Bleeding time, clotting time, hemogram, and capillary fragility tests were normal. Blood Kline was negative.

Histologic examination showed a normal epidermis and numerous foci of infiltrate in the corium. The cells were principally lymphoid and occurred in groups, especially around tiny capillary vessels. There were a few dense aggregates of cells. In the upper corium were scattered histiocytes, which were filled with yellowish-brown granular pigment, shown by special stain to contain hemosiderin.

Treatment has consisted of superficial x-ray therapy, ascorbic acid, and rutin. Clinically there appears to have been some improvement.

DISCUSSION

DR. J. E. RAUSCHKOLB: The question arises as to whether the pigmentation is part of the diabetic picture or would it have appeared if she did not have diabetes? It is limited to the anterior tibial areas. When we saw her last fall for the first time she had the typical reddish colored lesions. Since the first of the year there has been practically no therapy. Another interesting thing is that many of the lesions look like they might have been produced by scratching. Her injections of insulin are on the thighs, where she does not have any lesions. Her diabetes is fairly well regulated. I did inject potassium ferrocyanide in one of the lesions with the idea of trying to get a positive test for iron. It was negative.

In the literature there was only one article that Dr. Barnes found concerning fragility hemorrhage in the young diabetic, but in all those cases, a series of something like 60 or 70, the diabetes in young persons has been present for 20 years. In our patient it has only been present for two years. Most of them have arthritis. I thought this case was interesting from the diabetic standpoint.

DR. G. H. BARNES: One case reported by Becker in 1931 was similar to this—a 37-year-old man with pigmentation over the ankles and extending over the pretibial areas to the knees in a diabetic who had hemochromatosis. According to the history, he developed this pigmentation about 10 years before, at the age of 27.

Case for Diagnosis (Lichenoid Eruption Associated with Mediastinal Tumor). Presented by DR. JOHN A. GAMMEL, S. I. SATO, and J. L. SECREST for the Department of Dermatology, Western Reserve University.

R. V., a 59-year-old woman, was admitted to University Hospitals one week prior to presentation. Fifteen months ago, one month after the death of her husband, she bruised her left shin and subsequently developed an eruption involving the entire leg, with pain, redness, swelling, chills, and fever. She received 600,000 units of penicillin and sulfadiazine. One week later a fairly generalized erythematous eruption developed, which was pruritic. There also were elevated, hard, wart-like excrescences, which suggested to the physician previous arsenical medication. With local medication this eruption cleared completely during the course of about six months.

Last December the patient noticed generalized pruritus. Four weeks later a generalized eruption developed, which has since become worse. The process is claimed to be similar to the one she had late in 1951. During the past two weeks she lost much of her hair.

The patient had a hysterectomy 19 years ago, a thyroid operation 9 years ago, and ligation for varicose veins 8 years ago. She took barbiturates for 10 months for insomnia, but has taken none during the past two months. There are no known allergies.

The patient appears nervous and apprehensive. There is a generalized rather diffuse erythematopapular eruption. Over the knuckles, the knees, and the shoulders there is lichenification. In addition, on the abdomen, the inside of the thighs, wrists, and in the popliteal spaces are elevated, hyperkeratotic, rupioid lesions, 4 to 5 mm. high and 5 to 15 mm. in diameter. They are loosely grouped.

After the application of cold cream with coal tar solution these hyperkeratoses softened and became flatter, revealing a purplish base, suggestive of lichen planus. The top of her head is almost completely bald. The tongue is red and smooth, and there are fissures and crusts in the corners of the mouth. The vulva is reddened and swollen, and there is a profuse thick vaginal discharge, which shows no Neisseria organisms.

The hemogram was normal, except for 4% eosinophilia. Urinalysis was normal, except for numerous white blood cells. Total proteins were 5.8 gm., the albumin 3.9 gm., and the globulin 1.9 gm. per 100 cc.

The electrocardiogram showed auricular fibrillation.

Radiographs of the chest revealed a smooth circular area of increased density, extending from the midmediastinum into the right thorax. At various points along this mass there were flecks of calcification. After repeated studies, including fluoroscopy and radioactive iodine injection, no definite diagnosis could be made. Thymoma, dermoid or branchiogenic cyst were considered, but other tumors could not be ruled out. An exploratory thoracotomy was refused.

Histologic sections showed moderate hyperkeratosis and irregular acanthosis, with verrucous hyperplasia. The granular layer was prominent. There was liquefaction degeneration of the basal layer. A band-like infiltrate of lymphocytes and polymorphonuclear leucocytes was present in close approximation to the epidermis.

Treatment has consisted of high vitamin intake and local applications, with some improvement. The heart is being digitalized.

DISCUSSION

DR. H. HECHT: What type of chest tumor has the patient?

DR. J. L. SECREST: The tumor type has not been determined, but the x-ray department thinks that a thymoma or lymphoblastoma is most likely.

DR. J. A. GAMMEL: When I saw this patient in my office for the first time about 9 or 10 days ago the skin lesions, which now somewhat suggest lichen planus annularis, were elevated about twice as much—5 to 6 mm. In some areas they were verrucous. After a tar ointment was repeatedly applied in the hospital the lesions diminished in thickness, giving the picture I do not remember having seen before. There was redness of the tongue, probably due to vitamin B deficiency, and leucorrhea with a severe vulvitis. I certainly could not, even now, call this a typical lichen planus.

In the hospital they found a tumor in the chest, and I think that this might be the type of eruption associated with a malignancy similar to the one I reported last year (Gammel, J. A.: Erythema Gyratum Repens, A. M. A. ARCH. DERMAT. & SYPH. **66**:494, 1952).

I remember when I was a resident here many years ago Dr. Cole sent in a patient, in whom he suspected a lymphoblastoma, with a bizarre eruption. However, I did differential counts for a number of weeks and months and they were always normal. Six months later that patient was brought in in the terminal stage and died of lymphosarcoma. I therefore question the diagnosis of lichen planus annularis. We are dealing with a lichenoid eruption associated with a tumor in the mediastinum.

DR. J. R. DRIVER: I agree with Dr. Gammel on the interpretation of this eruption. I think it is a prurigo-like exanthem seen with some of the lymphoblastomas, particularly Hodgkin's disease. However, I think it is a lymphosarcoma rather than Hodgkin's disease. As Dr. Gammel mentioned, we had another patient with lymphosarcoma who presented somewhat the same picture.

Urticaria Pigmentosa. Presented by DR. S. I. SATO and DR. J. L. SECREST, for the Department of Dermatology, Western Reserve University.

Case for Diagnosis (Necrobiosis Lipoidica Diabeticorum?). Presented by DR. CHARLES S. BERRY and DR. MORTON A. SHAW for the Department of Medicine, Crile V. A. Hospital, Cleveland, Consultants, Dr. Allen E. Walker and Dr. John J. Stewart.

Micropapular Tuberculid. Presented by DR. H. N. Cole, DR. J. R. DRIVER, DR. H. N. COLE JR., and DR. PAUL V. CHIVINGTON JR.

Lichen Planus et Acuminatus Atrophicans (Feldman). Presented by DR. JOHN E. RAUSCHKOLB and DR. GILBERT N. BARNES.

Case for Diagnosis (Lichen Nitidus?). Presented by DR. H. N. COLE, DR. J. R. DRIVER, DR. H. N. COLE JR. and DR. PAUL V. CHIVINGTON JR.

Pyoderma Gangrenosum Associated with Ulcerative Colitis. Presented by Dr. S. I. SATO and DR. J. L. SECREST for the Department of Dermatology, Western Reserve University.

Chronic Monocytic Leukemia. Presented by DR. S. I. SATO and DR. J. L. SECREST for the Department of Dermatology, Western Reserve University. (Follow-up on a case previously presented to the Society as mycosis fungoides.)

Epithelial Nevi. Presented by DR. GEORGE H. CURTIS and DR. K. H. BURDICK.

Lupus Erythematosus Profundus. Presented by DR. GEORGE M. STROUD.

Dermatophytosis Pedis and Onychomycosis of Feet. Generalized Dermatophytid? Keratoderma Palmaris et Plantaris Vs. Psoriasis. Presented by DR. R. K. GARDNER, DR. G. W. BINKLEY and DR. H. H. JOHNSON.

Lymphangioma Cavernosum. Lymphangioma Simplex. Presented by DR. ALLEN E. WALKER and DR. JOHN J. STEWART.

MANHATTAN DERMATOLOGIC SOCIETY

Samuel M. Peck, M.D., *President*

George M. Lewis, M.D., *Secretary*

April 14, 1953

Reticulohistiocytoma. Presented by Dr. George C. Andrews.

B. M., a woman aged 49, noticed small red spots on the inner aspect of the thighs and axillae in August, 1951. These subsequently spread to involve the face, neck, and trunk. The lesions were asymptomatic. Three years ago the patient underwent a right radical mastectomy, followed by deep x-ray therapy. There is no history of arthritis. She has had a number of gold injections, which caused some pruritus of the arms and legs, and has taken Alophen (contains aloin, extract of belladonna, ipecac, and phenolphthalein) about once a month. She visited the Mayo Clinic, where a diagnosis of reticulohistiocytoma was made.

There are numerous widespread, discrete, elevated, reddish-brown papules varying from 1 to 6 mm. in diameter, arranged in fairly symmetrical distribution, notably in the axillae, groins, and about the mouth. The surfaces are glistening, and the lesions appear semitranslucent. There is no scarring. Clinically, the lesions suggest the lichenoid type of sarcoid, or multiple xanthoma. No superficial lymphadenopathy is found.

Urinalysis was normal, and serologic reactions for syphilis were negative. A biopsy read by Dr. Hamilton Montgomery was reported as showing large histiocytic cells simulating the cells in ganglioneuroma and occurring as giant cells. Bodian's stain was negative for Nissl granules, thus ruling out ganglioneuroma.

The patient was given cortisone, 75 mg. daily, with temporary improvement. Hydrocortisone (Hydrocortone) ointment applied locally was also of benefit, but she continued to develop new lesions. A few were successfully removed by desiccation.

DISCUSSION

Dr. Paul Gross: I cannot deny the resemblance to xanthoma, but the lesion is so unusual in its appearance that the diagnosis as presented would probably be proved correct by biopsy.

Dr. John W. Dougherty: Clinically, they appeared to me to be clusters of noduli cutanei.

Dr. Wilbert Sachs: I am unacquainted with this term, but the picture under the microscope does not look like the picture in the textbook. Clinically, the lesions suggest noduli cutanei. I should like to study those slides more carefully.

Dr. David Bloom: I cannot offer a diagnosis, but I am impressed with the similarity of the eruption to that seen in the photograph of the case of multiple ganglioneuroma reported by Montgomery and O'Leary (Arch. Dermat. & Syph. **29**:26 [Jan.] 1934).

Dr. Samuel M. Peck: The clinical picture is so at variance with my concept of what is reported as reticulohistiocytoma that I wonder if it is not worth while to take another biopsy. The lesions in the axillae were so superficial.

Scleroderma. Presented by Dr. George C. Andrews.

F. B., a woman aged 44, has complained of tightness of the skin of the face, V area of the chest, and arms for the past six months. Three months prior to the onset of the cutaneous symptoms she had pleurisy which was treated with penicillin. She had been well up to that time and had had no other serious illnesses.

On the face, neck, and arms there is a drawn tightening of the skin, which also involves the fingers, making it impossible to form a grip of the hands. There is a slightly brownish shiny appearance of the skin. On the chest there is a band-like area of hard shining skin. The blood pressure was 120/80. The white blood cell count was 14,400, which has now come down to 7,500. The erythrocyte sedimentation rate was 39 mm. in one hour, which has now come down to 25 mm. The urinalysis was normal.

In December the patient was given oxytatracycline (Terramycin) and testosterone propionate (Perandren), 25 mg. intramuscularly, twice weekly. Tripelennamine (Pyribenzamine) was given

daily, 200 mg. One month ago she was started on wheat germ oil (Denamone, 6 capsules daily) therapy. She also has taken one grain of thyroid daily. Softening lotions and creams have been used, and she has taken hot baths daily. Symptomatically she has improved considerably, although there is still a great deal of tightening of the skin.

DISCUSSION

DR. DAVID BLOOM: In cases of generalized and rapidly progressive scleroderma the administration of cortisone is indicated, in my opinion. It enables the patient to move around instead of being confined to bed and suffering intolerable pain at the slightest movement.

DR. SAMUEL M. PECK: I have treated a number of cases with cortisone and corticotropin (ACTH), and when the drug is discontinued the disease immediately relapses. Because of complications which are often serious, I do not give the steroid hormones unless the disease is fulminating. I have seen cases as extensive as this in which, after administration of dihydrotachysterol, the patient could open the mouth and had better flexion of the fingers, although the sclerotic process was unaffected. There is very little danger from proper administration. I have also had cases that seem to respond fairly well to large doses of vitamin E. The last report from the Lahey Clinic recommends sympathectomy in the hands of an expert. I have not followed enough cases to be able to evaluate them, but I am certainly against long-continued use of the steroids.

DR. PAUL GROSS: Because of the distribution and the slight involvement of the fingers, I would diagnose it as progressive diffuse scleroderma rather than acrosclerosis. The differentiation stressed by the important work of O'Leary is necessary because of prognosis and therapy. I would give the use of dihydrotachysterol first choice in this case and would use cortisone only if there is rapid progression. As far as the use of cortisone in acrosclerosis is concerned, I would definitely advise against it.

DR. MAURICE J. COSTELLO: I was under the impression that the patient had acrosclerosis; she could not move even her fingers, and there were no normal markings over the joints. When the shoulder girdle is involved, with the upper extremities and chest, I think it is in the class of acrosclerosis. The patient even has Raynaud's phenomenon, which is frequently seen in this disease. The patient I presented both at this society and the New York Dermatological Society was given a high protein diet and diphenhydramine (Benadryl) and had a very favorable response. I have the dubious distinction of having been the first to use dihydrotachysterol in the treatment of the disease. The first case was reported in the ARCHIVES, and the patient made a remarkable recovery and is still alive, but I have treated several since then, with complete failure.

DR. FRANK C. COMBES: I agree with Dr. Costello and disagree with what Dr. Bloom has said. I have never seen results with dihydrotachysterol. Some cases do improve spontaneously, so it is hard to evaluate. I have had some good results with diphenyhydramine. It is very important that these patients be given a high nitrogen diet, with massage of oil into the skin and passive movement. They used to rub patients with mercurial ointments. Dr. CoTui treated several patients with a high nitrogen diet and demonstrated that improvement was directly proportional to the nitrogen balance. All these patients have a negative nitrogen balance and improve on a high nitrogen diet.

DR. GEORGE M. LEWIS: I thought until I read the article in *J. A. M. A.* that sympathectomy was coming into disrepute, and I am wondering whether the consensus here is that it is a good procedure. At New York Hospital there have been patients with whom brilliant results have not been had, and I think it is not considered good therapy at that institution. From my knowledge, I do not think is is justified. I agree with Dr. Costello that diphenyhydramine is the one drug with which I have had much success, and I would certainly advise its continued use.

DR. GERALD F. MACHACEK (by invitation): I was under the impression that she has not only scleroderma but myositis. There is certainly definite disability and atrophy. I agree that she ought to have a high protein diet, diphenyhydramine, physiotherapy, and I would also give cortisone.

DR. DAVID BLOOM: I do not wish to give the impression that I consider cortisone a panacea for all types of scleroderma. Many cases undergo spontaneous remission, and all kinds of remedies are wrongly thought to be the cause of the remission. But in the malignant cases of scleroderma, I do not know of any remedy which will do as much good as cortisone.

DR. GEORGE C. ANDREWS: We shall perform examinations of internal organs for sclerodermatous changes. The patient is in poor financial circumstances so we have hesitated to do this, but shall manage in some way.

Hypertrophic Lichen Planus. Presented by DR. JOHN W. DOUGHERTY.

J. D., an Italian-born man aged 53, has had a nonpruritic verrucous linear scaly symmetrical eruption on the hands, palms, arms, prepuce, legs, and feet for the past 13 years. The eruption began on the legs and in the course of five years spread to the sites now involved. On two occasions ulcers appeared on the calves and healed, leaving scars. The eruption has been static for the past eight years.

Penicillin therapy was given at another hospital, dosage unknown, with no change. A keratolytic ointment rapidly removed the scales, leaving the eruption as it is seen now.

Cultures from the nail, sole, and arm showed no growth. The Mazzini reaction was negative on two occasions. A blood bromide determination was negative. Biopsy revealed hypertrophic lichen planus.

DISCUSSION

DR. WILBERT SACHS: The microscopic picture is classic for that disease.

DR. GERALD F. MACHACEK (by invitation): I thought of lipotroteinosis. It would be worth while to perform a big biopsy, even though it does look like a very occult lichen planus.

DR. MAURICE J. COSTELLO: I think the eruption does not look at all like verrucous lichen planus and think lipoid proteinosis should be considered. There is no itching, and I think it is impossible to have lichen planus without some degree of itching, and especially lichen planus of the hypertrophic type.

DR. ANTHONY N. DOMONKOS (by invitation): I should like to suggest epidermodysplasia verruciformis, in which the lesions, although not erythematous, are primarily verrucous. Epidermodysplasia verruciformis may develop at any time of life and may involve the urethra, and here I believe there is a lesion on the penis.

DR. WILBERT SACHS: I think the biopsy ruled out that possibility. Hypertrophic lichen planus frequently does not itch. I have seen a patient with a solitary lesion that lasted for many years without itching.

Case for Diagnosis (Poikiloderma?) Presented by DR. PAUL GROSS.

M. C., a woman aged 48, born in Russia, has lived in Brazil since the age of 16. She noticed a cutaneous eruption at the age of 20, which spread gradually. It did not itch, and she was not treated for it. For the past two months an eruption has involved the palms.

The patient has had many illnesses, including cholecystitis, and recently has been suffering from psychomotor vertigo. A hysterectomy has been performed.

There is widespread eruption over most of the shoulders, extensor surface of the arms and elbows, hips, and lumbar region. The skin in the affected areas shows cigarette-paper-like atrophy. In addition, there are small guttate papules resembling parapsoriasis, and in some areas telangiectases can be noted. On both palms are scaly psoriasiform patches, and in the surrounding normal skin are a few minute deep-seated vesicles.

A blood cell count was normal, and the Mazzini reaction was negative. The erythrocyte sedimentation rate was 24 mg. in one hour.

Biopsy from the left shoulder revealed an atrophic epidermis, wth edema of the deeper layers. Parakeratosis was present. In the subepidermal cutis was a striking infiltration of mononuclear cells. Many of the vessels were greatly dilated. The slide had the characteristics of poikiloderma.

DISCUSSION

DR. WILBERT SACHS. I do not think there is such an entity as generalized poikiloderma; I think it is the forerunner of another disease.

DR. DAVID BLOOM: This seems to be a typical case of poikiloderma vasculare atrophicans. Some of these cases may change after many years into manifest mycosis fungoides, but as long as there are no changes present, the term idiopathic is justified.

DR. GERALD F. MACHACEK (by invitation): I thought that was the diagnosis histologically, but after I looked at the patient I would go along with Dr. Bloom and say we must observe her for beginning lymphoblastoma.

DR. ANTHONY C. CIPOLLARO: There is no question that this is a typical case of poikiloderma, as described by Jacobi. Whether or not this person is going to develop something else we can not tell, but, certainly, cases of poikiloderma have existed for 20 to 30 years without lymphoblastoma developing.

DR. PAUL GROSS: I presented this patient because for many years I thought that this type of poikiloderma was a manifestation of mycosis fungoides. On the basis of the history and findings in this and two other cases I have observed in recent years, I tend to believe there is an entity of poikiloderma distinct from mycosis fungoides and not related to dermatomyositis.

Porokeratosis (Mibelli). Presented by DR. GEORGE M. LEWIS.

L. R., a man aged 33, born in Italy, has been in the United States for three years. For 14 years he has noted lesions on the hands, left thigh, and scrotum. There is no associated pruritus, and no treatment has been given. The patient's father has a similar condition.

Examination reveals brown circinate lesions with a clearing center and firm base. The border is elevated, verrucous, and indented.

DISCUSSION

DR. DAVID BLOOM: This is a typical case of porokeratosis of Mibelli, and the histology will undoubtedly confirm the diagnosis. In addition to this type there are two others, namely, the plaques with a serpiginous irregular blackish outline which may show pronounced hyperkeratosis in the center, and the linear type which resembles a nevus.

DR. SAMUEL M. PECK: This is one of the best cases I have ever seen.

DR. GEORGE M. LEWIS: After seeing several cases presented with this diagnosis by Dr. Barker in which the features were not easily recognized, I am delighted to demonstrate this patient whose lesions are so typical.

Squamous-Cell Epithelioma with Eosinophilic Reaction. Presented by DR. GEORGE C. ANDREWS. (Previously presented at the Metropolitan Dermatological Society by Dr. Anthony N. Domonkos.)

C. DeL., a man aged 30, states that a small lesion appeared on the chin in July, 1952, and gradually spread to cover a large area. When the patient first came to see me on Dec. 16, 1952, the lesion measured 5 cm. in diameter and had a verrucous nodular appearance, with a considerable amount of exudation and some deep-seated follicular pustules. No glands were palpable. A biopsy performed in the South in August was read by Dr. Wilbert Sachs, who made a diagnosis of an infection thought to be due to a bacteria or fungus. The patient had had penicillin injections, sulfonamides, and chlortetracycline (aureomycin) daily for 6 weeks. There was considerable improvement with all these forms of therapy, but the lesion persisted and grew. On Dec. 19 material was gathered for fungus examination. Direct examination revealed no fungi, and cultures were negative for deep-seated fungous infection. A larger and deeper specimen was removed for biopsy and was reported both by Dr. Machacek and by Dr. Sachs as a "squamous cell epithelioma, well differentiated." Accordingly, radiotherapy consisting of 500 r was given to the lesion daily for 10 treatments, making a total of 5000 r at 100 kv., half-value layer, 1.4 mm. Al. The last treatment was given on Jan. 9, 1953. The patient was observed on March 9, at which time the chin was healing well. About four weeks ago he developed an enlarged lymph node on the neck, which was removed surgically. Biopsy reported a very unusual reaction, since there was a massive infiltraton of eosinophiles which made up the lymph node pulp in its entirety. There were also multinucleated giant cells. Metastatic carcinoma was ruled out, and it was felt that it was a granulomatous type of inflammatory reaction. This slide was examined by Dr. G. F. Machacek and by Dr. Arthur Purdy Stout. Both felt that it was an unusual reaction, and Dr. Machacek referred to E. H. Kettle's book "The Pathology of Tumors," in which he mentions identical reactions associated with squamous-cell epitheliomas, especially of the lips. In these cases, the glands have an eosinophilic infiltration.

At present the chin lesion is well healed and appears to have no further activity. A white blood cell count was performed this afternoon and showed a total of 8,500, with polymorphonuclear leucocytes 70 (mature 70, immature 0), lymphocytes 28, eosinophiles 1, basophiles 0, and monocytes 1. The red blood cells appeared normal.

DISCUSSION

DR. WILBERT SACHS: I am glad to know that you get an eosinophilic infiltration of the lymph nodes in squamous-cell epithelioma. I am wondering whether it is not the result of the infection the patient had, the cause of which is unknown. There is no question about the squamous-cell epithelioma.

Case for Diagnosis (Dermatitis Medicamentosa Due to Sulfamerazine, Persistent on a Light-Sensitivity Basis?). Presented by DR. MAURICE J. COSTELLO.

Angioma Racemosum. Presented by DR. GEORGE C. ANDREWS.

Case for Diagnosis (Mycosis Fungoides? Paraphoriasis en Plaque?). Presented by DR. PAUL GROSS.

Case for Diagnosis (Lichen Planus? Erythema Multiforme?). Presented by DR. ORLANDO CANIZARES.

Parapsoriasis en Gouttes. Presented by DR. ADRIAN BRODNEY.

Erythema Annulare Centrifugum. Alopecia Areata. Nevus Verrucosus Linearis. Presented by DR. ANTHONY C. CIPOLLARO.

Parapsoriasis en Plaque. Presented by DR. ADRIAN BRODNEY.

Case for Diagnosis. (Lupus Erythematosus?). Presented by DR. JACK WOLF.

Hydradenitis Suppurativa. Presented by DR. GEORGE C. ANDREWS.

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Stanton B. May, M.D., President

Fred F. Feldman, M.D., Vice-President

Irving A. Lewe, M.D., Secretary

May 19, 1953

Keratosis Follicularis (Darier's Disease) of Bullous Type (Benign Familial Pemphigus)? Presented by DR. KURT LINDSTROM.

Mrs. E. G. is a 27-year-old woman. At the age of 11 years, asymptomatic papules started appearing on the sides of her neck. There has been a slow increase in the number of papules and plaques ever since. The areas most prominently involved at the present time are the neck, upper trunk, palms, and soles. There are no known similar dermatoses in any of the patient's relatives. The patient also has tinea versicolor, which is clearing up with topical sodium thiosulfate.

The pathologist, Louis H. Winer, M.D., reported the microscopic examination of the biopsy specimen taken from the lesion on the central back as follows:

"Biopsy of the lesion of the back reveals a series of discrete lesions scattered along the surface of the epiderm often in relationship to the excretory ducts of sebaceous glands and hair follicles characterized by edema separation of cells, formation of cystic spaces, and the development of atypical cells, with hyperchromatic nucleoli either attached to the margins of these lesions or desquamated in their lumina. In such areas typical parakeratosis is encountered in widened follicles. Associated therewith is a very mild nonspecific perivascular chronic inflammation in the superficial corium.

"Diagnosis: Darier's disease of bullous type (benign familial pemphigus)."

DISCUSSION

DR. MEYER BERKE: From a clinical standpoint, I do not think the eruption was consistent with benign familial pemphigus. From a pathological standpoint, it probably, to my mind, fitted the keratosis follicularis (Darier's disease) better than the bullous keratosis follicularis. I think we could conceive that the keratotic lesions could clinically fit the picture of keratosis follicularis too. I would be willing to accept that diagnosis.

DR. IRVING A. LEWE, Montebello, Calif.: I agree with Dr. Berke. I thought that, clinically and histologically, this fitted the picture of keratosis follicularis.

DR. HAROLD C. FISHMAN: I agree with Dr. Lewe and Dr. Berke. I think this is definitely a keratosis follicularis, both histologically and pathologically. Hailey and Hailey's disease is a vesicular disorder. No vesicles had been noted in the past, according to the patient's history. Lesions on the palms and soles never occur in Hailey's disease. These lesions were papular, and confluent, not as much as customary, but definitely fitting the clinical concept of a Darier's disease. In one section, histologically, there were definite corps ronds and grains, which do not occur in Hailey and Hailey's disease. I agree with the last two discussers.

DR. FRED F. FELDMAN: Two clinical features to further substantiate the diagnosis of keratosis follicularis in this patient are the hyperkeratosis of the palms and soles and the lichenoid papules on the dorsum of her hands and fingers.

DR. KURT LINDSTROM: I had hoped that some of the men might have some therapeutic suggestions.

DR. MAX POPPER: I believe this is a case of Hailey and Hailey's disease and not of keratosis follicularis. The elementary lesions of keratosis follicularis are papules composed of friable horny material, bluntly conical in appearance, and of dull earthy color. By confluence these papules form plateaus with a rough, slightly verrucous surface. None of these characteristics were seen in the case presented. The histological picture is compatible with the diagnosis of Hailey and Hailey's disease.

There is a fundamental difference between keratosis follicularis and Hailey and Hailey's disease. Keratosis follicularis is based on a congenital dysfunction of certain, individual cells or group of cells in the basal-cell layer. The changes encountered in keratosis follicularis within the basal-cell layer have been pointed out by Brunauer in his article in Jadassohn's handbook. Some of the basal cells, but not all of them, have lost the ability to form normal prickle cells. Instead, they develop into cells without prickles, known as corps ronds. This peculiarity of the basal cells is transmitted to the daughter basal cells, lasts in the person for a lifetime, and runs in families. As the corps ronds do not form prickles they lose their connection with surrounding prickle cells; in this way open spaces known as lacunae, or clefts, are formed. Surrounding these lacunae are prickle cells which have retained their prickles and are perfectly normal in shape and in staining properties.

In Hailey and Hailey's disease we are dealing with an inflammation of the skin which affects the Malpighian layer, causing the loss of prickles that is acantholysis. The resulting clefts are not sharply demarcated but are more diffuse in character, pervading the entire prickle cell layer in the involved areas. The typical lesion shows clear spaces in which lie groups of cells, without prickles, some of them otherwise normal in appearance, some of them resembling corps ronds. At the border of the clefts we find prickle cells, many of which are unconnected with one another and arranged in an irregular pattern, scattered about like dice on a table. Hailey and Hailey's disease has a tendency toward complete remissions, whereas in keratosis follicularis lesions do not completely disappear.

As this condition is characterized by an inflammatory reaction resulting in the loss of prickles the name dermatitis acantholytica would more properly describe this entity. As clinically some of these cases, as for instance the presented case, do not exhibit bullae or vesicles throughout their whole course, it is unfortunate to have affixed the name of pemphigus to this condition.

DR. SIDNEY J. ROSE: I agree with the diagnosis of keratosis follicularis in this case. Cases have been reported to respond to high doses of vitamin A. I would suggest aqueous vitamin A intramuscularly in high doses, supplemented by oral high doses of vitamin A, as a trial.

DR. WILLARD L. MARMELZAT: I should like to reiterate what Dr. Rose has just said about giving vitamin A. One should give it parenterally as well as orally. Just about two years ago, I presented identical twins with pityriasis rubra pilaris to this society. According to the history, one had the disease three months and the other three or four weeks. Biopsies were presented, and everyone in the society accepted them as typical cases. These children were 8-year-old girls. It was decided after discussing the case to use vitamin A, by mouth, for a period of several months. The disease remained *in status quo* in one and progressed in the other; whereupon they were put on intramuscular vitamins, and the oral vitamin administration stopped. I have reported similar cases like this of vitamin A deficiency, in which oral ingestion produced no beneficial results, but, parenteral administration cleared lesions of typical vitamin A deficiency. I now give you a follow-up report on these two girls. Their lesions cleared after several months, and they

were then placed on vitamin A orally just to try to keep them clear. I saw them several months ago, and they had remained free from this illness. In spite of my telling the mother to stop using the vitamin A, she will not. She uses it in small doses.

DR. MURRAY ZIMMERMAN: What do we consider adequate vitamin A? It never states in the articles whether they are using water-soluble, synthetic vitamin A, or whether they are using fish oil vitamin A, 80% of which can be recovered from feces. I should like to know. Also, do any other members of this society favor using thyroid and hydrochloric acid with the vitamin A? An editorial in the *Journal of the American Medical Association* May 30, 1948, cited research indicating that for vitamin A absorption and utilization thyroid is necessary. Since reading that article, I have used thyroid with vitamin A, but I don't know about the hydrochloric acid. I think it has been suggested that it be given, too. When you talk about "large doses" and "small doses" of vitamin A, what do you mean, Dr. Marmelzat?

DR. WILLARD L. MARMELZAT: That is a good question, a question that I ask myself and ask others, too. Some physicians in this society consider 200,000 units of vitamin A aqueous, daily, as a large dose. This is given by many men in this community. Some pediatricians are afraid to give patients 1,000 units of vitamin A per day. There is no standard answer. I consider 100,000 units per day for several months a large dose for an adult. I do not like to give that much. I try to get down to 50,000 units and eventually then to 25,000 units of aqueous, water-soluble vitamin A. In a child, it should be scaled down. Most untoward results with vitamin A therapy have occurred in children.

DR. KURT LINDSTROM: Thank you very much for the discussion and suggestions. I apologize for the slide that was damaged in transit. I am sorry that Dr. Louis Winer was not able to attend this meeting. I purposely left out my own clinical impression of keratosis follicularis of Darier's. I am grateful for the lively discussion.

Tinea Manum et Onychomycosis (Unilateral); Tinea Pedis et Onychomycosis. Presented for therapeutic discussion by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Localized Urticaria Pigmentosa(?) Presented by DR. HAROLD PRICE.

Cavernous Hemangioma on Nose. Presented for therapeutic suggestions by DR. IRVING A. LEWE.

Idiopathic Nonthrombocytopenic Purpura. Presented for etiological and therapeutic discussion by DR. HERBERT A. FISHBEIN.

Parapsoriasis? Psoriasis? Presented for diagnosis by DR. STANTON B. MAY.

Recurrent Basal-Cell Epithelioma of Nose, Postradiation. Presented for discussion of management by DR. STANTON B. MAY.

Lupus Erythematosus? Neurodermatitis? Presented for diagnosis by DR. STANTON B. MAY.

NEW ENGLAND DERMATOLOGICAL SOCIETY

Mildred Ryan, M.D., *President*

Joseph Goodman, M.D., *Secretary*

Feb. 11, 1953

Dermatomyositis. Presented by DR. WALTER F. LEVER, Boston, and DR. MERLE HAANES, Beverly, Mass.

G. W., a 55-year-old, white, married woman, developed a diffuse erythema of the face and neck a little more than two years before presentation. A diagnosis of contact dermatitis was made, but the eruption persisted. Six months later, patchy erythema developed on the hands and forearms. A little over a year before presentation, a diagnosis of subacute disseminated lupus erythematosus was made. Biopsy of the skin revealed changes which were consistent with this diagnosis, but the lupus erythematosus cell was not found. One year before presentation, the patient developed marked muscular weakness, dysphagia, periorbital erythema and edema, and widespread erythema and scaling of the trunk and extremities. A second biopsy of skin and muscle revealed changes which were consistent with a diagnosis of dermatomyositis.

Oral cortisone was started nine months before presentation, with marked improvement. Weakness largely disappeared. The changes in the skin improved but did not disappear. Dysphagia persisted. The dosage of cortisone varied from 250 mg. to 150 mg. a day.

DISCUSSION

DR. WALTER F. LEVER, Boston: This case was presented to show what relatively good results could be obtained with cortisone in a patient with severe dermatomyositis. An attempt has been made not to suppress the disease entirely but to give enough cortisone to keep the patient going. When admitted for the second time to the hospital, this patient was so weak that she could only lie in bed. At first, larger doses of cortisone were given. Lately, we have been able to reduce the dose to 150 mg. of cortisone per day, and the patient has been able to keep going. This is important in cases of dermatomyositis, because once the patient becomes bedridden a diffuse atrophy and muscle contraction results. Treatment with cortisone in such cases can be life-saving. How long this patient will have to continue with this present dosage no one can say, but I am glad to report that so far this patient has had no side-reactions, except for slight confusion while on the higher doses. Lately, she has been doing a fairly good job as a housewife.

DR. BERNARD APPEL, Lynn, Mass.: I should like to ask Dr. Lever if he finds any difference between corticotropin (ACTH) and cortisone in treating patients with dermatomyositis.

DR. WALTER F. LEVER, Boston: A number of children with dermatomyositis are being followed at the Children's Hospital. It seems to make no difference whether corticotropin or cortisone is given to these children.

Pemphigus Vulgaris: Complete Remission for Eight Months. Presented by DR. CHESTER N. FRAZIER, Boston.

Lichen Ruber Moniliformis. Presented by DR. WILLIAM R. HILL, Boston.

?Lupus Vulgaris. Presented by DR. WILLIAM J. MACDONALD, Boston.

?Boeck's Sarcoid. Presented by DR. WILLIAM J. MACDONALD, Boston.

Alopecia Universalis. Presented by DR. MAURICE M. TOLMAN, Boston.

Pityriasis Rubra Pilaris. Presented by DR. CHESTER N. FRAZIER, Boston.

Guttate Parapsoriasis. Presented by DR. PAUL J. CATINELLA, Boston.

Nevus Syringadenomatosus Papilliferus. Presented by DR. BERNARD APPEL, Lynn, Mass.

Perforating Ulcer. Presented by DR. BERNARD APPELL, Lynn, Mass.

?Prurigo Mitis. Presented by DR. MAURICE M. TOLMAN, Boston.

Subacute Disseminated Lupus Erythematosus. Presented by DR. MAURICE M. TOLMAN, Boston, and (by invitation) DR. JOHN H. COX, Chelsea, Mass.

?Bacterial Dermatitis ?Atypical Dermatitis Herpetiformis. Presented by DR. ARTHUR S. SPANGLER, Boston.

Folliculitis Decalvans. Presented by DR. WALTER F. LEVER, Boston, and DR. MERLE HAANES, Beverly, Mass.

Pemphigus Foliaceus. Presented by DR. CHESTER N. FRAZIER, Boston.

Mildred Ryan, M.D., President

Joseph Goodman, M.D., Secretary

April 8, 1953

Tinea Capitis Caused by Trichophyton Violaceum. Presented by DR. SYDNEY J. ALLMAN, Boston.

NEW YORK DERMATOLOGICAL SOCIETY

George C. Andrews, M.D., President

Maurice J. Costello, M.D., Secretary

March 24, 1953

Case for Diagnosis (Contact Eruption Caused by Denture? Bullous Lichen Planus? Erythema Multiforme? Pemphigus Vulgaris?). Presented by DR. MAURICE J. COSTELLO.

C. McL., a 66-year-old woman of Irish birth, has had a vesiculobullous eruption confined to the hard palate for the past two months. The eruption consists of two elements: The portion just posterior to the upper teeth is made up of thick-walled closely aggregated pinhead-sized and larger vesicles. Proximal to this is an eruption consisting of 8 or 10 larger thin-walled ruptured bullae, with denuded epidermis and pellicle-like fringes. Cortisone had no effect on the eruption.

The Wassermann reaction of the blood is negative, and complete blood cell count and urinalysis are normal. She has been taking Alophen (contains aloin, extract of belladonna, ipecac, and phenolphthalein) pills for years, but the elimination of their use did not influence the eruption. A course of oxytetracycline (Terramycin) was of no avail. The fact that her upper denture

was not inserted for a week caused no improvement, although when it was applied to her left forearm as a patch test the result was positive. The patient was questioned thoroughly regarding the ingestion of drugs and said she had not taken any recently.

DISCUSSION

DR. CARL T. NELSON (by invitation): I think this patient has a contact stomatitis due to the acrylic denture. She has a positive patch test to the denture on the skin. This is rather uncommon, since sensitivity of the mucous membranes usually does not go hand in hand with sensitivity of the skin.

DR. ANTHONY N. DOMONKOS (by invitation): I agree with the diagnosis. The lower plate seemed to be of a different material; it was gotten at a different time and was made by a different dentist. She has no eruption nor any form of dermatitis on the lower gums.

DR. GEORGE M. LEWIS: It looks like contact stomatitis, the doubt only existing because of the long duration. One should always be suspicious of pemphigus, as the presenter mentioned.

DR. ANTHONY C. CIPOLLARO: I agree with the diagnosis of contact stomatitis and think the evidence of a positive patch test substantiates it.

DR. WILBERT SACHS: It is unusual for vesicles or bullae to remain intact in the mouth. If it were a contact eruption one would not expect them to remain intact. If it were on the skin I would accept that diagnosis, but in the mouth I am doubtful for that reason.

DR. LESLIE P. BARKER: I think it is a contact eruption and that the patient should take out the plate for the time being. A culture and smear should be taken to eliminate the possibility of primary or secondary moniliasis.

DR. GEORGE C. ANDREWS: I agree with Dr. Barker. We had a patient recently with two linear streaks on the gums where the plates rested. I thought it was definitely a contact stomatitis, but we took scrapings for Candida, which were positive. It was painted with gentian violet and cleared up, and the patient is wearing the plate without any trouble. It is worth while to look for Candida in these cases.

DR. MAURICE J. COSTELLO: I also agree with Dr. Sachs that it is rare for one to see unruptured thick-walled bullae in the mouth. Those in the front of the mouth have been there for 10 days without change. Sometimes one has to incise them for relief, as in bullous lichen planus of the mouth.

Case for Diagnosis. Blistering Eruption of Face, Scalp, and Neck. Presented by DR. GEORGE C. ANDREWS.

M. M., a woman aged 49, has had a blistering eruption on the sides of the face, scalp, and neck for the past three years. She was treated at the Skin and Cancer Hospital, where a biopsy revealed a deep-set pustular dermatitis. She received cortisone, penicillin, chlortetracycline (Aureomycin), and oxytetracycline (Terramycin), being helped temporarily by cortisone.

She first consulted me on Jan. 29, 1953, at which time there was a vesicular and bullous eruption which covered the scalp, temples, sides of the face, and neck. The early blisters were small and rather deep and firm, but those that had been present for some time had become flaccid and superficial. According to the patient, the evolution of the blisters from beginning to end was a matter of several weeks. The early firm little blisters looked herpetic, and some of them were in clusters, like those of herpes simplex. Some areas were ulcerated and covered by bloody crusts and looked as if they had been scratched. There were also crusted lesions on the backs of the hands. The buccal mucosa was entirely normal, and the rest of the body showed no involvement. There was slight swelling of the glands on the left side of the neck along the angle of the jaw, but these were not tender.

My clinical diagnosis was a usual type of virus infection, such as described by Lane and Lynch, belonging in the group called Kaposi's varicelliform eruption or possibly a type of dermatitis herpetiformis, for which reason I prescribed sulfapyridine, 2 gm. daily. This caused the eruption to disappear rapidly, and there was great improvement for three weeks, when the patient returned with a severe attack of herpes zoster of the right side of the neck and face, accompanied by fever and swelling of the lymph glands of the right cervical region and at the angle of the jaw. At this time the leucocyte count was 7,000, with a normal differential count.

The urinalysis was normal. The temperature was 100.2 F. by mouth and the pulse 100. Sulfapyridine was continued, but Protamide (a stable aqueous colloidal solution of a specially processed proteolytic enzyme) injections were begun for the herpes zoster. With this treatment the herpes zoster has largely disappeared, although there is still pain and tenderness in the right cervical region and right side of the face.

DISCUSSION

DR. FRANK C. COMBES: After all the study this patient has had, it is difficult to give a definite diagnosis, but I think three diseases should be seriously considered: first, localized dermatitis herpetiformis (Duhring's disease), second, the bullous type of lupus erythematosus which is suggested by a few lesions on her scalp, and, third, an unusual virus infection, as the presenter suggested, in the nature of an eczema vaccinatum or Kaposi's varicelliform eruption, but definitely not either of these diseases.

DR. GERALD F. MACHACEK: The histology certainly was not that of lupus erythematosus. It was definitely that of a pustular lesion. One hesitates to call it dermatitis herpetiformis, although it could be that, but I think there is a pyodermic element.

DR. WILBERT SACHS: The two diagnoses given clinically were the two I thought of microscopically. I asked if there had been an elastic tissue stain because I thought of bullous lupus erythematosus and possibly dermatitis herpetiformis, and also pyoderma of some type. I was not sure.

DR. L. P. BARGER: I could not make a diagnosis of dermatitis herpetiformis on the present eruption. The fact that it improved after sulfapyridine could suggest that diagnosis, although pyoderma or bacterid must be ruled out.

DR. FRANK E. CORMIA: I think the possibility of pyoderma is good. I do not know whether sustained antibiotic therapy has been given, but would suggest that the lesions be cultured and tested for sensitivity to antibiotics, and then a fair trial of the proper one be given. There is some possibility of virus disease, but it would seem unlikely that a virus disease of the type of Kaposi's varicelliform eruption could persist and recur over such a period of time. Possibly the patient later will develop a few vesiculobullous lesions on the trunk or even on the extremities.

DR. CARL T. NELSON (by invitation): I think that a possible actinic sensitivity should also be considered.

DR. MAURICE J. COSTELLO: Taking that cue, the patient has most of the eruption on the face, the V of the neck, and the scalp. The eruption was halfway between that of lupus erythematosus and pemphigus, which would be pemphigus erythematosus. The woman looks sick, in addition to the fact that the eruption is in those locations.

DR. GEORGE M. LEWIS: One other suggestion, based on a somewhat similar case, would be lymphoblastoma, especially leukemia, as an underlying process. Infections, both pyogenic and viral, may occur, and herpes zoster may be a symptomatic expression.

DR. ANTHONY C. CIPOLLARO: The only other thing to be considered is recurrent herpes, and another possibility would be factitial dermatitis. I should like to go along with what Dr. Lewis said in connection with one of the lymphoblastomas, and one manifestation would be localized vesiculobullous lesions. The patient should be examined for retroperitoneal nodes and an enlarged liver and should have careful blood study and bone-marrow examination. I do not believe in the concept of localized dermatitis herpetiformis. I have never seen any good evidence to substantiate that concept, and many cases presented as localized dermatitis herpetiformis have been cases of localized contact dermatitis.

DR. MAURICE J. COSTELLO: It would be interesting to institute treatment with Promacetin, which is less toxic than sulfapyridine. Dr. Fox showed a patient with dermatitis herpetiformis at the last meeting whose eruption has completely cleared with Promacetin (a sulfone derivative) therapy.

DR. GEORGE C. ANDREWS: The blood cell count and differential count were normal, and the lymph nodes showed no enlargement except as mentioned. That was on the left side first, which cleared with sulfapyridine, and then on the right side with the herpes zoster of the neck. The patient had received penicillin, chlortetracycline and oxytetracycline before she came to me. Sulfapyridine had an immediate favorable effect. The early lesions start as a cluster of

little firm vesicles, like herpes simplex, and then in the course of a week they form large flaccid bullae. That is a unique thing to see in an eruption like this and made me think of an atypical herpetic infection, like eczema vaccinatum or Kaposi's varicelliform eruption. I did think it might be a localized form of dermatitis herpetiformis and for that reason gave sulfapyridine, which seemed to clear it up.

Congenital Generalized Lymphangiectasia. Presented by DR. MAURICE J. COSTELLO.

Chronic Benign Pemphigus (Hailey-Hailey Disease) Generalized. Presented by DR. GEORGE C. ANDREWS. (Previously presented before the New York Dermatological Society February 24, 1948 [ARCH. DERMAT. & SYPH. **61**:355-357, 1950]).

A. M., a man aged 55, first consulted me on Oct. 2, 1947, because of a persistently recurring eruption of pus blisters in the axillae and on the chest, sides of the neck, and trunk. Later it became generalized. Biopsy from the right axilla showed chronic benign familial pemphigus, with some features of keratosis follicularis.

The axillae were treated by x-rays, and he was given alpha estradiol (Progynon), 6,000 intramuscularly each week, for one year. This caused improvement, and there were no signs of feminization. He also had some injections of dihydrostreptomycin. Since April, 1950, he has had no treatment and has been free from lesions.

Lupus Erythematosus with Panniculitis. Presented by DR. GEORGE C. ANDREWS.

Lupus Erythematosus with Panniculitis or Lupus Erythematosus Profundus. Presented by DR. GEORGE C. ANDREWS.

Trophic Ulcer of the Nose Following Nerve Operation for Tic Douloureux. Presented by DR. MAURICE J. COSTELLO.

Lupus Miliaris Disseminatus Faciei Associated with Possible Parapsoriasis Guttata. Presented by DR. MAURICE J. COSTELLO.

Sarcoidosis, Lichenoid Type. Presented by DR. GEORGE C. ANDREWS.

Porokeratosis of Mibelli. Presented by DR. Leslie P. BARKER.

Reticulum-Cell Sarcoma. Presented by DR. GEORGE C. ANDREWS.

Hookworm Infestation with Ulcers of the Shins. Presented by DR. J. LOWRY MILLER.

Erythema Multiforme Bullosum. Presented by DR. GEORGE C. ANDREWS.

Acne Scars Treated by Sandpapering. Presented by DR. GEORGE C. ANDREWS.

George C. Andrews, M.D., *President*

George M. Lewis, M.D., *Secretary*

April 28, 1953

Psoriasis. Pustular Psoriasis. Presented by DR. GEORGE M. LEWIS.

D. L., a nurse aged 45, developed vesicles and pustules in the paronychial region of several fingers in July, 1952. The eruption spread over the palms and later involved the soles. The paronychia was followed by dystrophic changes in the nails and at times partial evulsion. Numerous treatments have been employed. Cortisone was found to help keep the process in check, whereas x-ray therapy and various local measures were ineffectual.

Examination disclosed dry dystrophic nails suggestive of psoriasis. There were also patches of closely set deep vesicles and pustules on the fingers, palms, and heels.

DISCUSSION

DR. J. LOWRY MILLER: Pustular psoriasis is always difficult to diagnose. To me, these pustules do not exactly resemble those I think of as found in pustular psoriasis. I would think more of the diagnosis of pustular bacterid. The nail lesions could well be psoriasis, as could those on the face and neck. It would be difficult to make an absolute diagnosis of pustular psoriasis here.

DR. FRANK C. COMBES: I feel much the same as Dr. Miller. I prefer the term pustular bacterid, which means a little more than pustular psoriasis, but the nails do suggest psoriasis. I think the patient may have a disturbance of lipid metabolism, and I would do cholesterol determinations, phospholipid determinations, basal metabolic rate, etc. I would also look for fungi in those nails.

DR. PAUL E. BECHET: I also think the lesions resemble those Andrews describes under the name of pustular bacterid. I am never satisfied with the diagnosis of pustular psoriasis; I think there are no real pathognomonic lesions of significance, although it may be a microscopic diagnosis. I would like also to bring out the fact that our absent chairman has reported excellent results from finding remote foci of infection, and on correction of that element the lesions disappear. As far as I am concerned, it still is a bête noir of dermatology.

DR. ANTHONY C. CIPOLLARO: I prefer the name pustular psoriasis to pustular bacterid. I think these are separate entities or at least would so assume from a careful and detailed reading of the original descriptions of these two conditions. I, too, have had no particular good fortune in curing these patients by any method of treatment, including the removal of dead teeth or tonsils, or from a fat-free diet. I have obtained some improvement following treatment with wet dressings, and the use of chrysarobin ointment. However, I have failed to cure any of my cases. I believe some do get well, or we would see many more cases than we do.

DR. LESLIE P. BARKER: Without evidence of psoriasis elsewhere I cannot accept the diagnosis of pustular psoriasis. I think the diagnosis should be "pustular dermatosis" and a thorough search made for foci of infection. A white blood cell count should be done at the beginning of an outbreak to see if leucocytosis is present at that time. I would give internal antibiotic therapy.

DR. GEORGE M. LEWIS: If you examine the heels you see lakes of pus and closely set pustules. It is my impression that there is no difference between pustular psoriasis and pustular bacterid. The only way one can tell them apart is that if the patients get well after removal of the tonsils it is pustular bacterid, and if not, it is pustular psoriasis. Reliance on such a differentiation would hardly be tenable. I agree with Dr. Costello and Dr. Cipollaro that it is bad medicine to take tonsils out ad lib. We should not go overboard on the focus of infection theory, which is not in as much favor as formerly. Dermatitis repens is a pyogenic infection, whereas these lesions are sterile. There are all kinds of surface organisms, but no pathogens. Dermatitis repens almost always starts around a nail with an erythematous, deep-seated abscess that burrows and progresses. Quinacrine (Atabrine) hydrochloride is occasionally helpful, but I still obtain my best results from local application of chrysarobin.

Granuloma Annulare. Presented by DR. EUGENE F. TRAUB.

P. B., a woman aged 61, was first seen because of an unusually severe pruritus ani et vulvae that had been present for approximately five years and had failed to respond to treatment, including various types of injections and shock therapy. While the patient was under our observation and treatment for this disease an eruption suddenly appeared on both forearms, abdomen, and lower part of the back. This consisted of large papular lesions, with normal skin intervening. The papules were flat-topped, brownish-red, and about 3 to 6 mm. in diameter. The eruption was intensely pruritic and in some areas, because of scratching, tended to become confluent, although there was a tendency for the lesions to remain discrete even when closely packed together. Clinically the eruption suggested neurodermatitis, and this fitted into the patient's general background. Biopsy, however, was reported by Dr. Wilbert and Dr. Perry Sachs as granuloma annulare. Within the cutis, particularly in one area was granular degeneration. About this was a diffuse reaction containing epithelioid and multinucleated giant cells. The epidermis was somewhat regular and dry, but showed no significant changes.

This would be a very unusual example of the disease, as there were no annular lesions present. The eruption was extremely pruritic, and the location in most instances differed from that involved in the usual case of granuloma annulare. Many years ago the patient had some type of pulmonary disease which was at first suspected of being tuberculous, but was later proved not to be so.

DISCUSSION

DR. PAUL E. BECHET: It is difficult to make a clinical diagnosis. The lesions on the abdomen are flattish, sharply outlined, have a violaceous tint, and suggest lichen planus. The lesion on the back is entirely different. Certainly those on the chest had the appearance of the acute type of lichen planus, with large lesions.

DR. MAURICE J. COSTELLO: I think the patient has lichen planus, as evidenced by scratch marks, especially in the lumbosacral region, and I think a therapeutic test is necessary.

DR. GERALD F. MACHACEK: The granulomatous sections I saw rule out lichen planus. They are certainly suggestive of what we call granuloma annulare, but the patient also has a history of some pulmonary affection, and I do not know why it could not be a tuberculid. In fact, there is probably a series of peculiar granulomas which are called by other names because they do not fit in with granuloma annulare or necrobiosis.

DR. GEORGE M. LEWIS: It is interesting that the patient may have tuberculosis, as the older textbooks mentioned tuberculosis as an etiologic agent in granuloma annulare. There is at least one lesion on the abdomen that appeared typical of granuloma annulare, and that seems like the best diagnosis.

DR. WILBERT SACHS: We made a diagnosis of granuloma annulare, although we were not entirely happy about it. Tonight I think the patient shows more of the lesions of that disease.

DR. J. LOWRY MILLER: I agree with Dr. Machacek's idea of tuberculid.

DR. FRANK C. COMBES: One should never make a diagnosis before all the evidence is in, but if one looks at the patient clinically, no one here would have failed to make a diagnosis of lichen planus. There is the typical color, flat angulate papules with umbilication, a Koebner phenomenon, etc. The only explanation I have for the histologic report is that you have the wrong slide.

DR. EUGENE F. TRAUB: If I gave the impression that this woman had tuberculosis I should like to correct it. The diagnosis was made in Washington, but she has since been tested by some of the best chest men in New York, who claim she had not got tuberculosis. I thought of lichen planus, of course, but I believe after seeing her many times that it could be ruled out. I was certain Dr. Sachs would give me a diagnosis of neurodermatitis; the woman is highly neurotic, has had shock treatments, has pruritus ani et vulvae, and almost has to be restrained. I thought neurodermatitis would certainly fit into the picture. I have never seen a case of granuloma annulare that looked like this. Inside of a week or two she had hundreds of these discrete papules on the forearms and back, which gradually became confluent, and the itching was intense, which to my mind is against granuloma annulare. The first time I saw an annular lesion was today, and I am now willing for the first time to think the diagnosis of granuloma annulare is correct. Certainly it is the most widespread papular granuloma annulare I have ever seen.

Case for Diagnosis (Pemphigus Erythematosus? Localized Dermatitis Herpetiformis?). Presented by DR. MAURICE J. COSTELLO.

Lichen Planus. Presented by DR. GERALD F. MACHACEK.

Dermatitis Herpetiformis. Presented by DR. EUGENE F. TRAUB.

Lupus Erythematosus in a Patient with Active Tuberculous Nodes of the Neck. Presented by DR. EUGENE F. TRAUB.

Obituaries

HAROLD ORR, M.D.
1889-1952

Harold Orr, M.B., D.P.H., M.D., O.B.E., F.A.C.P., lately of Edmonton, Alta. Canada, died in Toronto on Dec. 26, 1952. He was returning from Athens, where he had attended, as a delegate from Canada, the meeting of the World Health Organization in October.

At the time of his death Dr. Orr was president of the Canadian Medical Association, sharing with William Allen Pusey, it is believed, the distinction of being the only dermatologist elected to the presidency of his national medical organization in an English-speaking country.

Dr. Orr was born in Toronto in 1889 and was a graduate in medicine of the University of Toronto Faculty of Medicine in 1911. He practiced in Medicine Hat, Alta., until he went to France in 1914 with the Canadian Expeditionary Force as a major in the Canadian Army Medical Corps. He served with distinction, being twice mentioned in dispatches, was made an Officer of the Order of the British Empire, and received the *Médaille des Epidémies* from France. After the war he studied under J. H. Sequeira at the London Hospital and became a member of the dermatological section of the Royal Society of Medicine. On returning to Canada he began his practice of dermatology and syphilology at Edmonton and became Clinical Professor of Dermatology at the University of Alberta Faculty of Medicine. He represented Canada at the International Dermatological Congress at Budapest in 1935.

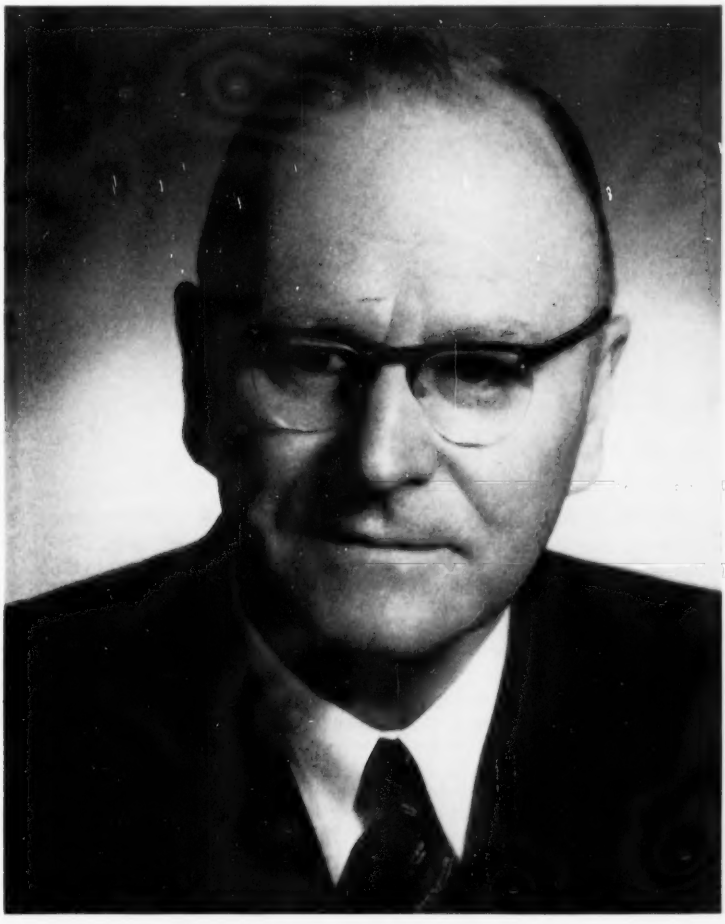
He maintained his association with the Canadian Army, and he was also in Public Health, becoming Director of the Division of Social Hygiene of the Alberta Department of Public Health. During World War II he was consultant in Venereal Disease Control to the Canadian Army, with the rank of lieutenant-colonel.

He was a Fellow of the Royal College of Physicians (Canada), a diplomate of the American Board of Dermatology and Syphilology, a Fellow of the American Academy of Dermatology, of the American College of Physicians, a Founding Fellow and past Vice-President of the Pacific Dermatological Association, and a member of the American Dermatological Association and of the Pacific Northwest Dermatological Society.

His contributions to medical literature were not numerous, teaching of his students, to whom he was much endeared, being his greater activity. He published however, among other papers, some of his mycological studies, and he was the first to describe a peculiar papular eruption of the hard palate in smokers (*Brit. J. Dermat.* **42:** 436, 1930), which he later referred to as leucokeratosis of the palate and which was presented as a classic study with colored plate and histological description.

Harold Orr had still other fields of interest and was a discriminating art critic, being especially active in promoting art appreciation in Alberta and developing the group of Western painters of the prairies and the foothills of the Rockies. His was

a warm and genial personality and his friends among colleagues and the lay community are numerous and widespread over many American and European countries. By them he is sadly missed, and in his more immediate circle he has left an irreparable gap.



HAROLD ORR, M.D
1889-1952

A few months before his death he had moved into semiretirement in Victoria, B. C., and established his home there, where he leaves a wife and daughter. But with his intense interest in his profession and medical organization and in public health matters, in which he was also specially qualified, it is not to be doubted that he would have given many more active years of service to his fellow men had he been spared.

D. E. H. Cleveland, M.D., Vancouver, B. C., Canada.

News and Comment

ANNOUNCEMENTS

Fourth Pollitzer Lecture.—The Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School announces the fourth Sigmund Pollitzer Lecture to be given by Stephen Rothman, M.D., Thursday, Jan. 21, 1954, at 4:00 p.m. in the Main Lecture Hall of the College of Medicine, 477 First Avenue, New York City. Dr. Rothman is Professor and Head of the Section of Dermatology and Syphilology, School of Medicine, University of Chicago. The title of his talk will be, "Some Physiologic and Endocrinologic Aspects of the Epidermis and Skin Appendages."

Books

Classics in Clinical Dermatology with Biographical Sketches. By Walter B. Shelley, M.D., Ph.D., and John T. Crissey, M.D. Price, $10.50. Pp. 485, with 111 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

It is a pleasure to recommend highly this volume to all dermatologists and to all medical libraries. There is contained within this book a vast amount of information concerning the great men of dermatology, including certain contemporaries. As the title indicates, the original descriptions of many of the dermatologic entities are translated completely or abstracted, together with a short biographical sketch of those physicians describing such entities. While the list is somewhat incomplete, the great majority of dermatologic diseases are included. As far as can be determined, the translations by the present authors of the original articles are accurate but not stilted.

Drs. Shelley and Crissey are to be congratulated for collecting these "classics" for the edification of our specialty and for all physicians. The reviewer notes, as all will who read this book, that in many instances our present-day concept of the entity goes well beyond and does not conform entirely with the original description.

The volume is excellently done typographically, and the photograph reproductions are adequate. It was a pleasure reading this book, and, once again, it is very highly recommended.

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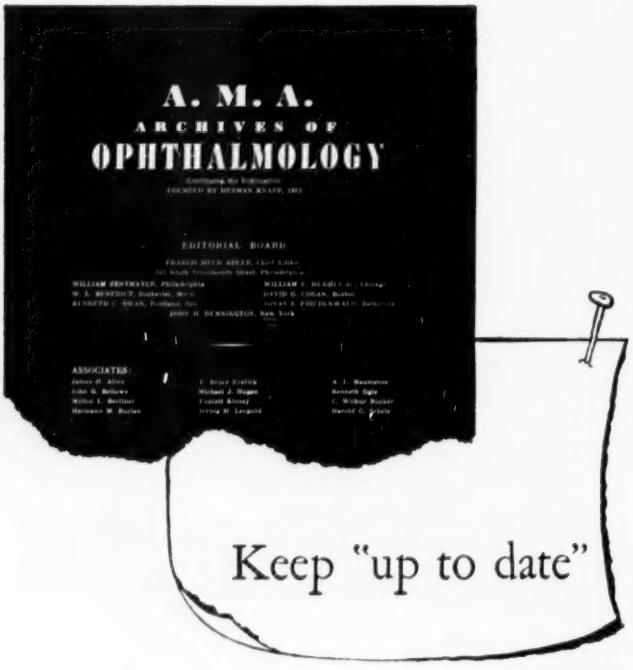
References:

1. Rothman, J. and Shapiro, A. L.: Med. Clin. N. Amer. 33:274-5, Jan., 1949.
2. Stieglitz, E. J.: Geriatric Medicine, p. 848, 1943.



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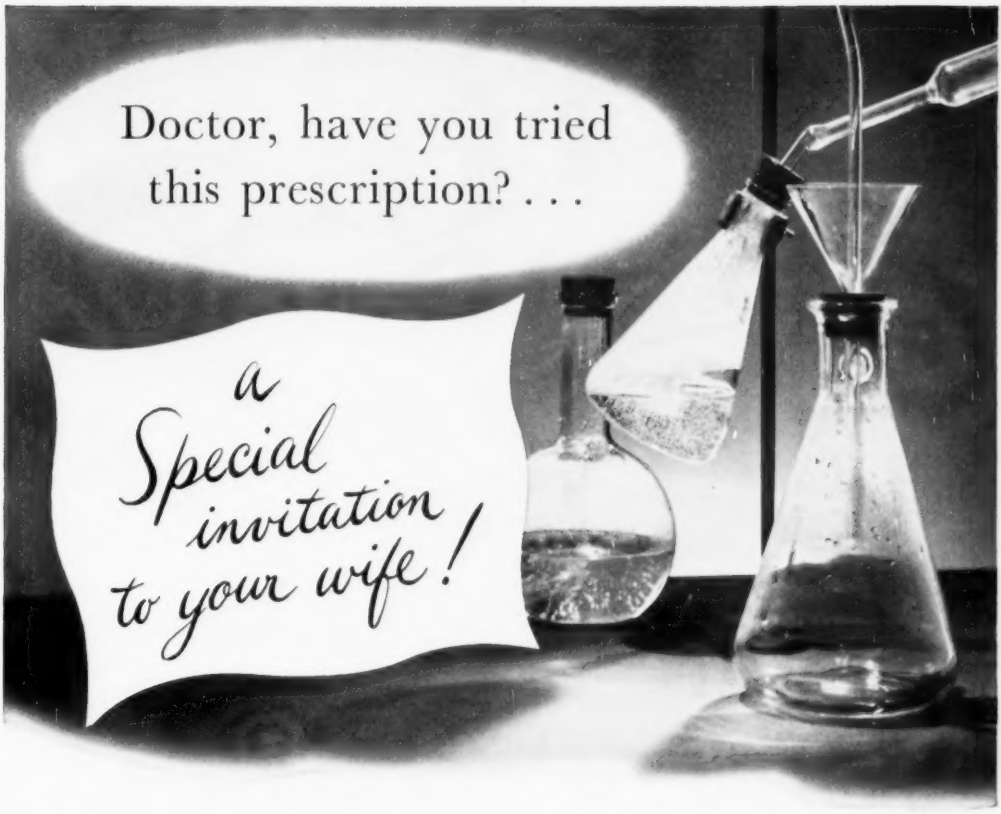

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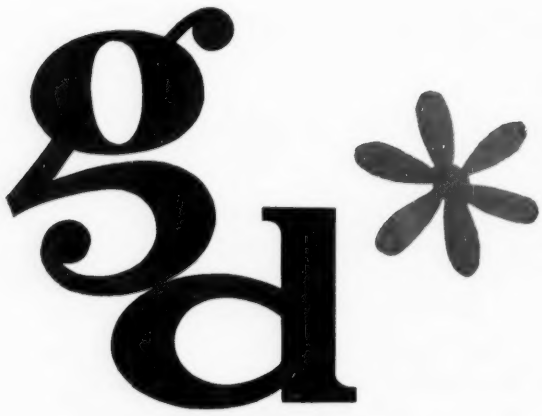

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